



A Current Review of Local Metronidazole Antibiotics for the Treatment of Periodontal Disease

Nora Azirah Mohd Zavi¹, Muhammad Lutfi Mohamed Halim¹, Mohd Yusof Mohamad^{1,3}

¹Department of Physical Rehabilitation Sciences, Kulliyah of Allied Health Science, International Islamic University Malaysia, Kuantan Campus, 25200 Kuantan, Pahang, Malaysia.

²Department of Fundamental Dental and Medical Sciences, Kulliyah of Dentistry, International Islamic University Malaysia, Kuantan Campus, 25200, Kuantan, Pahang, Malaysia.

³Cluster of Cancer Research Initiative IIUM (COCRII), International Islamic University Malaysia, Kuantan Campus, 25200, Kuantan, Pahang, Malaysia.

Abstract

Periodontal disease affects around 14.5% of the global adult population. It affects the tooth's supporting tissues, causing inflammation and tooth loss. Periodontitis treatment aims to prevent further disease progression by restoring the lost tissue and preventing bacterial infection. Nevertheless, periodontal breakdown may still occur post-treatment due to the periodontal pathogens. Antibiotics were utilized to control and prevent the infection. Local drug delivery system (LDD) is being developed to deliver the antibiotic due to its site-specific benefits. Metronidazole (MET) is widely used to treat periodontal infection following treatments due to its efficacy against obligate anaerobes and broad-spectrum characteristics. Despite its advantages, MET is attributed to systemic side effects. Therefore, this article aimed to review *in vitro*, *in vivo*, and clinical studies on the current local application of MET to treat periodontal diseases. 13 relevant research articles were analysed and provide valuable insights into the local application of metronidazole for periodontal treatment.

Keywords: metronidazole; local drug delivery; periodontitis, antibiotic

Abstrak

Penyakit periodontal menjejaskan sekitar 14.5% daripada populasi dewasa global. Ia menjejaskan tisu penyokong gigi, menyebabkan keradangan dan kehilangan gigi. Rawatan periodontitis bertujuan untuk mencegah perkembangan penyakit selanjutnya dengan memulihkan tisu yang hilang dan mencegah jangkitan kuman. Namun begitu, kerosakan periodontal mungkin masih berlaku selepas rawatan disebabkan oleh patogen periodontal. Antibiotik digunakan untuk mengawal dan mencegah jangkitan. Sistem penghantaran ubat tempatan (LDD) sedang dibangunkan untuk menyampaikan antibiotik kerana faedah khusus tapaknya. Metronidazole (MET) digunakan secara meluas untuk merawat jangkitan periodontal berikutan rawatan kerana keberkesanannya terhadap ciri anaerob obligat dan spektrum luas.

**Corresponding author:*

Mohd Yusof Mohamad

Department of Physical Rehabilitation
Sciences,

Kulliyah of Allied Health Science,

International Islamic University Malaysia,

Email: yusofkhs@iium.edu.my

Walaupun kelebihannya, MET dikaitkan dengan kesan sampingan sistemik. Oleh itu, artikel ini bertujuan untuk mengkaji secara *in vitro*, *in vivo*, dan kajian klinikal mengenai aplikasi tempatan semasa MET untuk merawat penyakit periodontal. 13 artikel penyelidikan yang berkaitan telah dianalisis dan memberikan pandangan yang berharga tentang aplikasi tempatan metronidazole untuk rawatan periodontal.

Kata Kunci: metronidazole; penghantaran ubat tempatan; periodontitis, antibiotik

1. INTRODUCTION

Periodontal disease or periodontitis is a major oral health problem in developed and developing countries. According to the Global Burden Disease Study (2019), approximately 14.5% of the global population suffered from severe periodontal diseases. The disease caused redness and swelling, gingival pain, bad breath, and the formation of periodontal pockets. In severe form, the tooth may migrate from the gums and alveolar bone causing tooth loss (Arigbede et al., 2012). Poor oral hygiene, stress, aging, alcohol, depression, smoking, and systemic conditions such as cardiovascular disease and diabetes are the aetiological factors of periodontal disease (Arigbede et al., 2012); (Nazir, 2018). The increase in cigarette smoking in developed and developing countries, together with obesity and diabetes, has increased the incidence of periodontitis. Tobacco has been identified as one of the major factors in promoting pathogenic bacterial infection, decreasing immune defense, and destroying periodontal cells such as gingival fibroblast, periodontal membrane, and periodontal ligament, which eventually leads to periodontitis (Petersen et al., 2005; Zhang et al., 2017). An adult individual has a higher risk of getting severe periodontitis with multiple tooth loss which can lower their nutrition intake, general well-being, and self-esteem, and increase healthcare costs (Tonetti et al., 2017). Periodontitis treatment aims to prevent further disease progression by restoring the lost tissue and reducing pathogenic bacterial infection. This can be achieved by a mechanical or surgical procedure. In certain individuals, periodontal breakdown may still occur despite the surgical or mechanical treatment due to the periodontal pathogens that invade and reside in periodontal tissue. Hence, antibiotics are required in the treatment of

infectious periodontal disease to control and prevent the re-emergence of periodontal pathogens (Mombelli, 2003). The antibiotics such as amoxicillin, clarithromycin plus omeprazole, penicillin, tetracycline, macrolide, and metronidazole are commonly used in periodontal treatment. Among the antibiotics used, metronidazole (MET) is one of the most promising antimicrobial agents for preventing periodontal infection due to its broad-spectrum activity, efficacy against obligate anaerobes, and minor side effects (Löfmark et al., 2010; Soares et al., 2012). Thus, systemic MET is prescribed before or after scaling, root planing, and periodontal surgery (Van Winkelhoff et al., 1996). However, long-term use of MET orally can cause nausea, gastrointestinal disturbances, seizures or numbness, and antibiotic resistance (Walker, 1996). Therefore, many researchers attempted to develop topical MET that can prevent systemic side effects while treating or preventing the spread of pathogens. The objective of this paper is to offer a narrative review of the current local application of metronidazole for periodontal treatment and evaluate its potential and limitation *in vitro* and *in vivo* research. In addition, this review also reported the current clinical use of local metronidazole.

2. MATERIAL AND METHOD

In order to obtain the most recent article on the local application of metronidazole for periodontal treatment, relevant research articles were searched from 2012 to 2022 in the English language using the keywords, metronidazole, local drug delivery, and periodontitis in the databases of SCOPUS, Pubmed, and Web of Science. Out of the 52 papers that were collected, 13 relevant original research articles were concise in this study, and the remaining article was

excluded due to irrelevant and duplicate titles.

3. RESULT

This study was performed to identify the local metro in terms of drug vehicle usage, biodegradability and biocompatibility of the system, drug release profile and clinical outcomes. In summary, the characteristic of the included studies was described in Table 1. Local metronidazole was successfully administered utilizing several vehicles, including film, sponges, gel, and fiber. By using various vehicles, the antibiotic releases occurred at different times and durations. The clinical study was discovered in this investigation by utilizing a gel containing 1% metronidazole during scaling and root planning (SRP) in cases of moderate-to-severe chronic periodontitis. It has been demonstrated that SRP combined with local antibiotic therapy produces better results than SRP alone (Sundaram et al. 2018). Thus, local drug delivery potentially delivers the antibiotic to the target sites, using lower doses by achieving higher concentration, and lasts for sufficient duration to be effective as it possesses high patient acceptability. Furthermore, local metronidazole potentially can be used as an alternative for the treatment of periodontal disease as it provides a high concentration of antibiotics in the affected area and thus treats the infection without systemic side effects and fewer chances of resistance development. Several studies are done on different drug delivery systems of metronidazole used in periodontal diseases and the researchers found positive results when the drug is applied locally rather than systemically (Paul et al., 2015; Re et al.,

2016; Nastri et al., 2019). Figure 1 below showed the various ways vehicles are successfully used. The capability of the vehicles to carry and release the drug is very crucial in treating periodontal disease. Different polymers served as basic materials of vehicles which influences their physical and mechanical properties and drug release. As can be observed, different vehicles with different materials have a varying release rate, with most of the drug in gel being highly eluted within 1-7 days, 2-5 days in films, and 7-28 days utilizing fiber mat. Even though the release rate varied, the vehicles demonstrated biocompatible, non-toxic, and good mechanical properties which can target directly periodontal pockets.

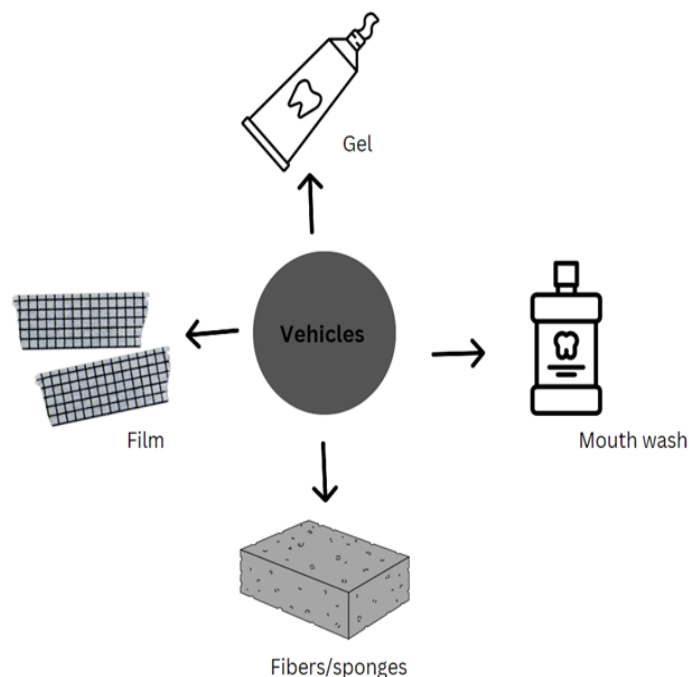


Figure 1. Current vehicles used to transport MET

Table 1. The summary of *in vitro* and *in vivo* studies using metronidazole (MET) from 2012-2022

Authors	Mechanism	Local drug delivery system	Findings
(Mirzaeei et al., 2021)	Electrospinning	Nanofiber	<ol style="list-style-type: none"> 1. Controlled drug release over 7-10 days in animal models. 2. Bio-compatible, non-toxic, and good mechanical properties.
(Pham et al., 2021)	Physical mixing	thermosensitive hydrogel	The hydrogels sustained release of metronidazole for 10 days
(Dhedage et al., 2020)	Modified solvent casting	Intrapacket film	<ol style="list-style-type: none"> 1. An initial burst release followed by a continuous release of more than 11 days. 2. Exhibited a biphasic drug release profile
(Azadi Boroujeni et al., 2020)	Casting	Mucoadhesive film	Releases the antibiotics up to 48 hours
(Léber et al., 2019)	Complex composition	An anhydrous lipid-based	<ol style="list-style-type: none"> 1. Sustain drug release with swellable and degradable systems. 2. Antimicrobial activity against six different strains of the pathogen that initiate periodontitis
(Laurén et al., 2018)	liquid molding	Mucoadhesive films	Rapid drug release of metronidazole observed in 30 minutes
(Rivis et al., 2018)	Lyophilisation of composite gels	Collagen/Strontium sponges	<ol style="list-style-type: none"> 1. The degradable system within 24 hours 2. Rapid release of drug at first 30- 60 minutes followed by gradual release over about 4 hours
(Hasan et al., 2020)	Clinical trial	Gel and mouthwash	<ol style="list-style-type: none"> 1. Significant reduction of periodontitis within four weeks 2. The gel is more effective than mouthwash in reducing clinical attachment loss and in

			reducing inflammatory biomarkers.
			3. No side effects reported
(Rangabhatla et al., 2017)	Thermoresponsive in-situ	Hydrogel	1. Mucoadhesive ability and biocompatible 2. Sustained the release of metronidazole over 24 h
(Mei et al., 2017)	Inverse lyotropic liquid crystalline (LCC)	Solution–gel	1. MIC of drug maintains for over 10 days in rabbits without a detectable drug in the blood. 2. Intra-pocket LLC system for local treatment of chronic periodontitis.
(Labib et al., 2014)	Solvent casting	Films	1. The burst release rate of metronidazole for the first 2 h then decreased. 2. Enhances the therapeutic effect of scaling and root planning (SRP) procedure than SRP alone
(Peerapattana et al., 2015)	Chemical mixing	Films	metronidazole slowly released from the matrices over 5 days.
(Reise et al., 2012a)	Electrospun	polylactide fibers.	metronidazole released up to the 28th day from fibre mats

4 DISCUSSIONS

According to the Centers for Disease Control and Prevention (CDC), periodontal disease is highly prevalent among adults worldwide with 47.2% of adults aged 30 years and older showed signs of periodontal disease and is commonly detected among men (56.4%) compared to a woman (38.4%). The primary cause of the disease is poor oral hygiene, which leads to the formation of microbial biofilm or dental plaque on the teeth. The gingiva inflames with no destruction of the alveolar bone or periodontal ligaments. Late treatment, genetic factors, and being immunocompromised can worsen the inflammation, causing bacteria to release various proteolytic enzymes and leading to

the destruction of tissue supporting the tooth (Gurav, 2014). The damage to the periodontal structure is due to protein-splitting that initiates neutrophil-secreted proteolytic enzymes and the activation of metalloproteinases in the connective tissue matrix. This is predominantly due to the periodontal pocket permitting periodontal pathogens in the domain which shifts bacteria flora with gram-negative anaerobic bacteria. The bacterial shift triggers an inflammatory response from the host (Herring & Shah, 2006). However, the pathogen that initiates the periodontal disease remains unclear. The plausible disease-causing gram-negative bacteria include *Porphyromonas gingivalis*, *Prevotella melanogenica*, *Prevotella*

intermedia, *Fusobacterium nucleatum*, *Actinobacillus actinomycetemcomitans*, *Bacteroides forsythus*, *Treponema denticola*, and *Selenomonas* species. Besides, gram-positive *Eubacterium* and *Peptostreptococcus micros* were also recently found in subgingival plaque in patients with chronic periodontitis (Herring & Shah, 2006; Mane et al., 2009). *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans* were reported as the causative bacteria that caused periodontitis (Gurav, 2014). However, among these organisms, *P. gingivalis* has been identified as the primary causative agent of chronic periodontitis. It was known as non-motile, asaccharolytic, obligate anaerobic Gram-negative bacteria that grows black-pigmented colonies on a blood agar plate (How et al., 2016). *P. gingivalis* secretes numerous hydrolytic, proteolytic, and lipolytic enzymes along with toxic metabolites. These enzymes are major virulence factors that promote the pathogen to colonize the periodontal tissue. Nevertheless, among all the enzymes secreted, *P. gingivalis* proteases are directly and indirectly involved with the colonization of the periodontal pockets, which leads to the destruction of periodontal tissue (How et al., 2016).

4.1 Health Implications

Periodontitis affects people's daily activities and well-being by causing pain associated with chewing due to missing and irregular teeth development (Shahzad et al., 2015). In chronic periodontitis, the epithelium lining of periodontal pockets becomes ulcerated, which permits pathogenic bacteria to enter the bloodstream or circulatory system. Thus, the bacteria may damage certain organs and contribute to systemic disorders. The presence of *Actinobacillus actinomycetemcomitans*, *Fusobacterium*

nucleatum-periodonticum-simiae group, *Prevotella intermedia*, *Prevotella nigrescens*, and *Tannerella forsythia* have been showed in atheromatous plaques from coronary arteries (Ohki et al., 2012). The pathogens that enter the bloodstream increase plaque build-up, which subsequently contributes to dilation of the arteries and cardiovascular diseases (How et al., 2016). Periodontal bacteria also have been detected in thrombi of patients with acute myocardial infarction (Winning & Linden, 2017). *P. gingivalis*, *S. mutans* was previously found to accelerate atherogenic plaque formation in a murine model and induce platelet aggregation, which leads to thrombus formation (How et al., 2016). Furthermore, periodontitis poses the risk to the fetus, resulting in premature labor or low birth weight (PLBW). Gram-negative bacteria produce endotoxins that stimulate the production of cytokines and prostaglandins which increase the incidence of labor, and proinflammatory mediators may get into the placenta barrier and cause fetal toxicity, which leads to preterm delivery and PLBW (Saini et al., 2010).

4.2 Treatment in Periodontal Disease

The term "periodontal medicine" has been known since 1990 and extensive research has been conducted since then (Mawardi et al., 2015). In the early phase, the goal of periodontal therapy was to prevent further disease progression to reduce the risk of tooth loss. It can be managed by non-mechanical treatment, including scaling and root planing to control periodontal inflammation. However, if the periodontal pocket is deep enough, surgery is required to restore periodontal attachment, including cementum, ligament, and alveolar bone. This would prevent the loss of teeth and the development of plaque (Graziani et al., 2018; Susanto et al., 2019). Adding systemic or local antibiotics to the

treatment of periodontitis is suggested to prevent the biofilm formation of pathogens after mechanical or surgical treatment.

4.3 The rationale of antibiotic therapy

The oral pathway is the most convenient route for drug delivery due to the ease of administration. However, undesirable side effects have been identified due to systemic antibiotic therapy. Antimicrobial resistance is recognized as a major side effect in the treatment of microbial infections (Upadhyay R et al., 2018). Several studies also reported poor oral drug delivery due to the first pass elimination across the intestine and liver (pH and enzyme) would limit the drug from entering the systemic circulation and reduce its bioavailability of the drug (Homayun et al., 2019; Zamani et al., 2017). Low drug delivery (LDD) of antimicrobial agents has gained interest among researchers due to higher concentration of drug at the site of action can be achieved despite using a lower dose of the drug. Furthermore, prolonged, and improper use of systemic antibiotics might lead to the development of resistant bacteria strains and unfavorable systemic side effects. The LDD can be retained in the periodontal pockets for a longer period without disrupting the oral cavity's microbial balance. It also can prevent the emergence of bacterial resistance and systemic effects while producing therapeutic effects (Hasan et al., 2020). Thus, LDD could be an effective way to control periodontal disease bacteria while preventing systemic side effects.

4.3.1 Topical antibiotic in managing periodontal disease.

Local drug delivery systems (LDD) can be non-biodegradable or biodegradable. For non-biodegradable systems such as implants, they must be removed or discharged from the pocket following

fulfillment of the drug release. Thus, the insertion of a non-biodegradable system is time-consuming, and the removal process may harm the new tissue (Reise et al., 2012b). Biodegradable systems are polymeric or protein in nature and undergo natural degradation in response to the gingival fluid. Examples of biodegradable systems include fibers, powders, strips, pastes, gels, and ointments (Southard & Godowski, 1998). Thus, by using the local delivery system the drug can pass the systemic circulation of the jugular vein and bypass the first-pass hepatic metabolism, leading to the high bioavailability of the drug (Graziani et al., 2018; Homayun et al., 2019). The environment of the periodontal pocket poses a huge challenge for LDD where an increased resistance of microorganisms in biofilm constitution occurred. Furthermore, the presence of the gingival crevicular fluid increases the clearance of the drug in the periodontal pocket (Zupančič et al., 2019). To successfully deliver the drug to the intended site, a few parameters must be achieved, including the drug must reach the site of action, sufficient concentration, and efficient drug release that lasts for a long time. Table 1. shows that different LDD system load MET and using fiber, film, and hydrogel, the drug successfully releases over a prolonged time. Other advantages include high antibacterial activity, excellent biocompatibility, and painless administration. An *in vivo* study showed LLC loaded with MET was safe for the local treatment of periodontitis in rabbits with no detectable MET in blood. The clinical study was done to identify the significant reduction of periodontitis within four weeks between mouthwash and gel. Today, LDD is preferred over the systemic method, as evidenced by previous study showing that the gel is more successful than mouthwash in reducing clinical

attachment loss and in reducing inflammatory biomarkers due to its site-specific administration (Hasan et al., 2020). Until now, patients have had access to a metronidazole gel that is available on the market.

4.3.2 Potential Application of Local Metronidazole

An infectious disease caused major death throughout the world. However, in the 20th, penicillin was discovered from mold culture as an antibacterial drug that has saved millions of people's life and since then more than 100 different antibiotics have cured minor to life-threatening infectious diseases (Soares et al., 2012). However, each antibiotic only works for certain types of bacterial infections. Antibiotic treatment of periodontitis aims to reduce infection after non-surgical or surgical procedures. Various systemic antibiotics such as tetracycline, penicillin, metronidazole (MET), and clindamycin have been used to minimize infection after dental surgery (Dodwad et al., 2012). Previous research suggests that MET could be an ideal antimicrobial agent for treating periodontal disease, particularly in patients who are allergic to penicillin and its derivatives (Léber et al., 2019). MET belongs to the nitroimidazole class of antibiotics that were used in the treatment of periodontal infection due to its broad-spectrum characteristic and its efficacy against obligate anaerobes (Van Winkelhoff et al., 1996). In 1960, MET was introduced to treat vaginal *Trichomoniasis*. Recently, it was employed on acute necrotic ulcerative gingivitis (ANUG) (Nastri et al., 2019). Instead of its ability to kill anaerobic bacteria, MET has been administered in the treatment of periodontitis because of its effective for patients with aggressive periodontitis (Rivis et al., 2018). To treat periodontal

disease, it is recommended to take 250 mg of MET three to four times per day for approximately ten days. However, systemic MET was linked to gastrointestinal intolerance, nausea, diarrhea, unpleasant taste, a furred tongue, and peripheral neuropathy (Van Winkelhoff et al., 1996). According to the World Dental Federation (FDI), approximately 10% of antibiotics are prescribed by dentists, and the World Health Organization predicts that by 2050, ten million deaths per year will result from the improper use of antibiotics, which can lead to antibiotic resistance. Furthermore, resistant bacteria can be transmitted from one person to another through contact and other modes of transmission (Khabeer et al., 2021). Thus, a low dose of MET is preferable to reduce the side effect on the gastrointestinal system as well as to minimize the chances of bacterial resistance (Zhang et al., 2017). Local drug delivery was introduced in 1976 by Goodson et al., thus, in the last 40 years, this system has gained the attention of researchers in formulating different antibiotics and anti-inflammatory agents in treating periodontal disease (Hasan et al., 2020). In a previous study, a lower concentration of metronidazole (5-20%) is locally sufficient to inhibit the growth of *Prevotella* spp., *Phyromonas gingivalis*, *Campylobacter rectus*, *Fusobacterium* spp., *Aggregatibacter actinomycetemcomitans*, *Eikenella corrodens*, *Capnocytophaga* spp., and *Streptococcus mutans* (Peerapattana et al., 2015). As a result, there is a growing interest in using metronidazole locally for periodontal disease treatment.

4.3.3 Limitation of topical antibiotic

The main challenge of the available local delivery systems is a lack of durability, rapid clearing of the drug from the periodontal pocket area due to the salivary flow and

outflow of gingival crevicular fluid, and short bioavailability resulting in inadequate therapeutic efficiency (Azadi Boroujeni et al., 2020). Thus, the success of locally delivered metronidazole is determined by using vehicles for releasing metronidazole such as mouth rinses, patches, fibers, gels, films, or sponges. These vehicles help release the drug contents in a controlled manner and keep the concentration of the drug at the right level in the attended area (Mirzaei et al. 2021). Second, the characteristic of vehicles such as biocompatibility and good mechanical properties, and non-toxic to the body, is very crucial to avoid any irritation or inflammatory reaction and reducing the administration frequency. Furthermore, the interactions between the drug and polymers might occur during the preparation and consequently altering its properties and disrupting the drug delivery system. Thus, for this issue, an investigation needs to be done to confirm there is no alteration of metronidazole when loaded into the vehicle. The short release of the drug also can be by using nanotechnology where the drug is loaded into the nanocarrier, therefore, increasing the bioavailability of drugs with controlled release properties and enhancing the antimicrobial activity of metronidazole. In short, the capability to control drug release at the target site is crucial in treating periodontal disease. In this study, the clinical study was only proven by using a gel with 1% metronidazole for the treatment of chronic periodontitis which requires frequent applications and leaves a bitter metallic taste. Thus, future clinical study is recommended using other vehicles such as fiber, film, and sponges which might reduce their application duration and taste.

5. CONCLUSION

There are several advantages of low drug delivery in treating periodontitis.

Metronidazole is a broad spectrum of antibiotics that is beneficial in preventing and reducing the bacteria related to periodontitis. Most significantly, a high dose of metronidazole is commonly applied via oral administration. However, LDD attains higher concentrations of the drug at the intended site of action using a lower dose compared to systemic therapy. Thus, this indirectly reduces and prevents systemic side effects and antibiotic resistance linked to oral use. In this study, the LLD reported can carry and release the drug within different time frames depending on the vehicles used. Thus, we strongly suggest the use of local metronidazole combined with scaling and root planning or surgical therapy to treat periodontitis. This indirectly can control the use of systemic antibiotics and elude the adverse effect and reduce worldwide resistance.

Recommendation for future research

To avoid the systemic side effects and development of resistance associated with the use of antibiotics, LDD methods have gained the attention of dentists to treat periodontal infections, in combination with scaling and root planning. However, further studies are still needed to recommend this novel system as a routine therapeutic modality for clinical use. The effects of these drugs in periodontal treatment need to be done thoroughly on larger patient populations in the future. Furthermore, it is recommended to use local metronidazole along with scaling and root planning or guided bone regeneration therapy depending on how serious the condition is to treat periodontal diseases. The development of bioresorbable, biodegradable, and medically approved materials that are convenient and economically viable for clinical use is still needed. Longer periods of drug release need to be considered in future studies and the effect of local application of metronidazole

on systemic disease conditions needs to be investigated. Further studies on larger patient populations are required to investigate more thoroughly the effects of these drugs and the value of these markers in local periodontal management. Furthermore, the advancement of nanomedicine and nano-based drug delivery has emerged as a promising delivery system recently and has successfully been applied to many pharma drugs. Thus, nano antibiotics and efficient drug release that lasts for a long time.

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Ethical Statement

There are no ethical issues in this study.

Conflict of interest

The authors have no conflict of interest.

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