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The current novel drug delivery system (natural and chemical composites) in dental infections for antibiotics resistance: a narrative review

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ABSTRACT

A mouth infection can also affect the teeth, the mouth tissues, and any other areas involved in the mouth. Biofilms formed by bacteria are the primary cause of mouth infections and other infectious diseases caused by bacteria. The most common dental problem is an infection or disease within the mouth. The term chronic infection is sometimes used to describe this type of problem. There is also the possibility that these discomforts may occur due to the presence of bacteria in plaque, which is responsible for causing inflammation throughout the body as a result of bacterial infection in the mouth. In many cases, antibiotics serve as a first-line treatment for mouth infections, especially those caused by bacteria, most commonly treated by antibiotics. It is common for antibiotics to be used orally, and they are absorbed into the body through their metabolism in the liver and kidneys. Antibiotic resistance, which is primarily caused by misuse and overuse of antibiotics, is also one of the most significant public health crises of the 21st century. With the help of new drug delivery systems, antibacterial resistance can be decreased in humans to maintain the effectiveness of antibiotics when they are used more frequently. By directly delivering antibiotics to damaged tissues and reducing undesirable side effects when administered systemically, antibiotic delivery systems enhance the efficiency of antibiotics in specific zones. Furthermore, several new delivery systems are being explored in an attempt to improve pharmacokinetics and pharmacodynamics, reduce bacterial resistance, and decrease dose times. As a result, antibiotics were delivered to tissues and biological fluids using an innovative delivery system. Research on some of the most prevalent dental diseases provides updates on antibiotic delivery systems that reduce antibiotic resistance. This review overviews oral infectious diseases, antibiotics effects, and the different delivery systems of these therapeutic approaches.

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Introduction

Dental infections usually occur in oral tissues, teeth, and surrounding parts. Also, dental infections resolve through drainage of spontaneous dental extraction or tooth gingival tissues (1-4). Complications of these infections happen from infection extension directly by the adjacent tissues into the neck and mediastinum and promising spaces surrounding the jaw. Possibly, oral infectious diseases can disseminate by the biological fluids, especially blood, to different organs and sites of the body, causing neurological disorders, thrombosis, and even bacterial endocarditis (5, 6). Periodontal conditions are considered one of the most prevalent disorders worldwide, have significant impacts on health and economic situations, and drastically decrease the quality of life consequences. The most common oral diseases in different countries are periodontal disease, oral cavity and lips cancer, tooth loss, and dental caries (7-13). Throughout history, humans have encountered numerous microorganisms, including bacteria, which have caused significant morbidity and mortality among various populations all over the globe. A powerful antimicrobial agent, penicillin, was available in the early 1940s. Hence, penicillin plays a vital role in treating many infectious diseases. Penicillin has become less effective due to excessive use due to the development of different types of resistance mechanisms by bacteria. Microorganisms with resistance to antimicrobial agents can survive and survive under the influence of antimicrobial agents (14). In addition to antibiotics, disinfectants, and food preservatives, there are several other types of antimicrobial agents that can be used to inhibit the growth of microorganisms, reduce their multiplication, or even kill them (15). It is recognized that there are natural, semi-synthetic,

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and synthetic agents with distinct mechanisms capable of causing significant metabolic and physiological effects. Examples include modification of cell wall synthesis, for example, β-lactams, and protein synthesis inhibition, such as Macrolides and tetracyclines. It is also known that sulfonamides inhibit the metabolism of the DNA and interfere with its replication, for example, Fluoroquinolones (8, 9, 16, 17).

Antibiotics are generally used in various dentistry circumstances, although the indications of systemic antibiotics are limited in periodontal and dental infections due to best-managed conditions through oral hygiene measures and intervention with the operation. The majority of antibiotic prescriptions are established based on bacteriological, clinical, and epidemiological features engaging in the application of limited ranges of broad-spectrum antibiotics for a short duration (18). As a rule, antibiotics have been used in the infected areas throughout local or systemic administration. Therefore, antibiotics can prohibit cell wall synthesis, RNA, mRNA, DNA, peptides, protein, or other vital molecules in pathogenic microorganisms, particularly bacteria. (19). Antibiotics are also prescribed in dental conditions for treatment or prophylaxis approaches. To prevent disorders as a result of oral flora distribution into different sites at risk in a host, prophylactic drugs such as antibiotics are routinely prescribed. In diverse cases, prophylactic approaches are considered to prevent bacterial endocarditis, where antibiotics are used as a treatment approach to ameliorate diseases of soft and hard surrounding tissues in the oral cavity after the failure of local debridement (20). The most reliable and effective pathway to access adequate concentration of antibiotics is systemic administration which affects subgingival flora elimination through the transition of drugs in the biological fluids (21). Antibiotics utilize at different rates of release (controlled or immediate release) by the systemic or local administration. However, there is increasing evidence that misuse of antibiotics will ultimately lead to the development of antibiotic resistance, complicating the efficient use of antibiotics in health care. Further, the insufficient availability of effective antibiotics reduces the possibility of preventing and treating health conditions involving immunity compromises, such as HIV, cancer, surgery, and diabetes (22). In fact, some antibiotics, such as tetracyclines, have been regarded to revolve around crevicular fluid at higher concentrations than those discovered in serum after the same dose of oral administration. Thus, the antibiotic can later connect to the surfaces of teeth (23). Antibiotics can penetrate the pocket and periodontal tissues by a serum that is applied systemically. Then they access the bacteria which are unreachable to the local therapeutic use of antibiotics or scaling instruments. Systemic usage of antibiotics is a promising method to suppress pathogenic microorganisms colonization in periodontal diseases (24). Therefore, this route of antibiotic administration prepares elimination of biofilms and prevents infections through periodontal pathogenic microorganisms that eradicate the colonize extra dental tissues or the subepithelial periodontal areas (25). A wide variety of microbial species are conducted in oral and dental infectious diseases that may accumulate in certain areas and change to biofilms. Consequently, biofilms contribute to the invasion of periodontal or dental tissues, shown in figure 1. Thus, there is require for novel systems that provide a specific profile of

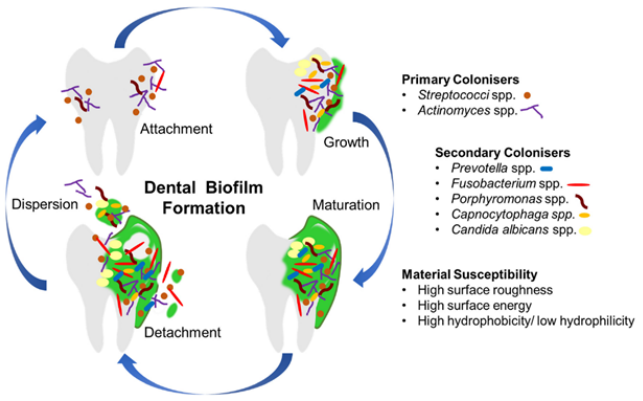

Figure 1. Overview of primary dental microbes and biofilm formation as a crucial part of dental infections (28).

antimicrobial agents without cytotoxicity and new antimicrobial drug delivery formulations have been examined in dentistry recently (26). It is appropriate to use drug delivery systems in periodontal pockets that are biodegradable and manageable such as mucoadhesive polymers preparing enhanced binding of mucosa and dosage forms. The most convenient therapeutic procedures for local delivery of antibiotics in periodontal pocket contain films, fibers, gels, injectable systems, implant, particulate formulations, and vesicular systems (27). This review overviews oral infectious diseases and antibiotics effects and different delivery systems of this therapeutic approaches.

Materials and Methods

Several databases were used in this review, including PubMed, SciFinder, ScienceDirect, and Google Scholar. As part of the first part of this research, extensive bibliographic research was conducted utilizing the following keywords "drug delivery system", "biomaterials", "dental diseases", "dental infections", "oral cavity", and "antimicrobials", as well as the related antibiotics, to complete the research. Of the 1287 articles found, 155 were approved to proceed to the writing phase, while the remaining articles were rejected due to their emphasis on delivery systems, the use of repeated information, or the lack of documentation. There is a focus on the evaluation of antibiotic and antibacterial substances, their administration, delivery system properties, and the effects of these substances in dentistry fields in the selected material. The selection of articles and patents is based on English language publications. After conducting the first phase of bibliographic research, the second phase of the research focused on each of the antibiotics and antimicrobial compounds. The following keywords are selected, “Tetracyclines”, “Clindamycin”, “Metronidazole”, “Gel”, “Nanoparticles”, “Films”, and “Microspheres”. Between June 2021 and July 2022, bibliographic research was conducted, covering works from 1977 to 2022.

Oral infectious disease

Oral conditions have been named one of the important public health problems among populations, with a special interest in their increasing prevalence in several low-income and middle-income countries, attached to broad economic, commercial, and social changes (29). Oral and periodontal diseases are categorized naturally into aggres-

sive and chronic. For instance, dental caries has various influences on toddlers or children but is a lifelong disease that persists into adulthood, adolescence, or even later in life. Oral diseases affect most impoverished members of society (30). Many diseases have significant influences on the hard and soft tissues of the oral cavity containing congenital anomalies, craniofacial diseases, and diverse infections. Moreover, oral infections have been known to have a main role in the presentation of various inflammatory diseases which have systemic effects, such as pulmonary diseases, cardiovascular diseases, and gastrointestinal disorders (31-34). Nevertheless, the major clinical disorders that are deemed to be worldwide public health priorities involve oral cancers, osteomyelitis, periodontitis, and PI (7, 35-39).

Peri-implantitis

PI is one of the pathological disorders taking place in dental implants surrounding tissues, attributed to inflammation in the progressive loss of supporting bones and the peri-implant mucosa. In Figures 2 and 3, properties of bacterial adhesion to dental implants and, afterward, bacteria aggregate and biofilms are demonstrated. Also, PI is an irreversible and progressive disease which are occurred in tissues around the soft and hard tissues of dental implants attended to resorption of bone, reduction of osseointegration, rising formation of pockets, and purulence (40). Inflammatory factors such as loss of bone, deep probing, and bleeding have other outcomes like implants that insert too deep. In addition, implant shape and type, kind of connection, superstructure and abutment material, and sort of prosthetic structure impact the peri-implant hard and soft tissues (41). Mombelli et al. have investigated the prevalence of peri-implant conditions recently that reported PI occurred in 10% of inserted implants and 20% of implanted patients. It points out that remodeling procedures of bone usually affect marginal bone loss throughout the first weeks after linking abutment that cannot be considered as PI, although the prevalence percentage has been explained with caution due to the variability of the analyzed findings (42). Thus, take a radiograph after superstructure insertion and regard the radiograph as a future assessment base of bone loss of peri-implant. In addition to infections around the implants in areas with deep probing depths, some cases of periapical PI lesions have been reported (43). Affecting implants are also determined with periapical radiographic radiolucency without or with accompanying clinical inflammation signs such as edema, redness, fistula, or/and formation of abscesses (44). For PI, various indicators/ risk factors have been suggested containing untreated periodontitis, periodontitis history, diabetes, smoking, inadequate care, level of bone-implant design, excess cement, and insufficient preparation of prosthetic therapy (45). From the clinicians' point of view, periodontitis history and untreated periodontitis have significant importance due to patients with periodontitis have been demonstrated to be treated properly do not have an increased risk of PI in comparison with susceptible non-periodontitis patients, while individuals with periodontal pockets during installation of the implant have a hazard for PI which is about four times more than non-sensitive patients or treated periodontitis individuals efficiently (46).

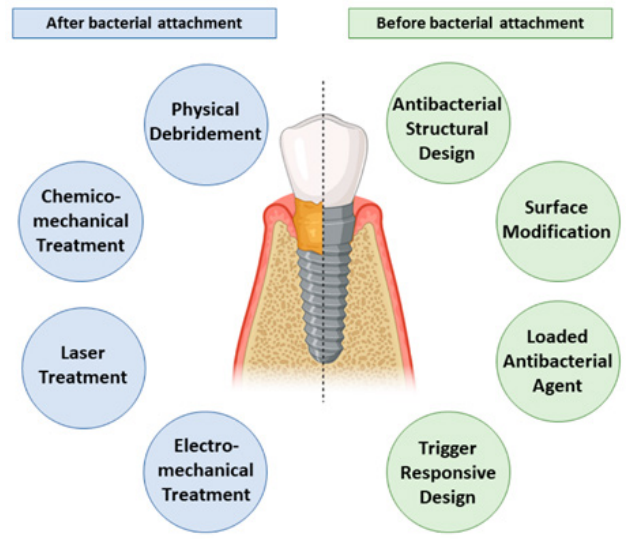

Figure 2. Properties of implants in the oral cavity (47).

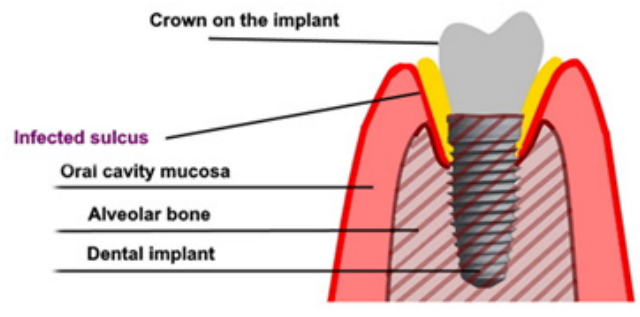

Figure 3. Graph of Peri-implantitis (48).

Periodontitis

Periodontitis is a complicated infection with various contributory and etiologic elements that can happen in childhood or often debuts in early adulthood and maybe later years (49). Also, periodontitis is a high prevalence of about 50% total with the most complex from influencing approximately 11.3% of people around the world is the 6th most frequent human condition (50). Periodontitis usually appear with one or more risk factors in patients although individuals with a wide range of disease severity may indicate identical hazards. Furthermore, some people with severe disorders, such as periodontitis which are appeared aggressively in juveniles, show some non-classic risk factors (51). The biofilms of pathogens adhered to the surface of the root in the subgingival area which is commonly resistant to chemical antibacterial compounds and the natural antimicrobial defense processes in the mouth (50). *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are crucial pathogens of aggressive periodontitis, although low content of the species may prohibit stable sites of disease (52). Periodontitis influences selected surfaces of teeth, scarcely the whole dentition, and can procedures the tooth apex while containing a near tooth dividing the same space, which is located interdental. The particular site of periodontal failure cannot be described through the accumulation of dental plaque and maybe through a complex bacterial and viral infection (53). Generally, chronic periodontitis has presented in adults and is associated with the level of local risk factors, principally calculus/plaque. This provides to develop steadily with exacerbation duration. Systemic disorders such as cardio-

vascular disease and environmental factors affect chronic periodontitis severity (54). On the contrary, aggressive periodontitis has various effects on the younger population, which are under 25 years, with the familial association and characterized by rapid destruction of adhesion and bone with no or little deposits of pathogens. Additionally, the majority of patients are systemically healthy, however, they have aggressive periodontitis (55).

Mandibular osteomyelitis

MO is a common infectious bone disease that tends to conclude soft tissue, periosteum, and adjacent cortex. Often, this type of osteomyelitis is restricted to the mandible probably, because of poor vasculature of the mandible in comparison with the maxilla and the complicated anatomy which base on a slim cortical plate and plenteous vascularity (56). Osteomyelitis is quite uncommon unless, in some cases, related to osteonecrosis medications or osteoradionecrosis. The most common etiologies of osteomyelitis in the jaw are traumatic and odontogenic, although abundant activity may have occurred. Generally, it has major impacts on patients affected by systemic disorders such as malnutrition, diabetes, immune insufficiency, cancers, and malnutrition because this type of infection is almost polymicrobial (57).

Lesions of osteomyelitis in the mandible should be categorized as synovitis osteomyelitis and bacterial osteomyelitis, pustulosis, acne, and SAPHO (osteitis) syndrome despite the fact they are scarce chronic infections and inflammatory diseases (58). Usually, oral surgery, mandibular fractures, and dental infections are causes to the appearance of MO in most cases which is characterized by various pathogens such as *actinomyces*, *staphylococcus*, and *alpha-hemolytic streptococcus* (59). Bacterial osteomyelitis clinical indications are promoting and osteolytic radiographic alteration with the periosteal response of lamellar type. The osteomyelitis lesions are simply treated through antibiotic administration. In osteitis syndrome, MO is commonly distinguished through a complex radiographic paradigm with resorption of external bone, enlargement of bones, and the periosteal response of solid type. The osteomyelitis appearance in another bone, skin disorders such as psoriasis, acne, and pustulosis, and arthritis firmly recommended the syndrome (58). The procedures of inflammation contain tissue necrosis, sclerosis, resorption, and malignancies. In some cases, surgical debridement requires antibiotic therapy to complete the treatment of patients suffering from osteomyelitis. Also, the prevalence of MO has gradually decreased because of the improvement in oral health and different antibiotics administration (60). However, osteomyelitis has usually occurred in patients with immune system problems and is commonly attributable to pathogens inoculation into the bone due to trauma, surgical processes, utilization of chemotherapeutic medications, or dental infections (61).

Gingivitis

Gingivitis is the main disorder in humans that conclude inflammation in gingiva areas and may be reversible if the therapeutic approaches are managed correctly. Various treatment methods involving alteration of dietary lead to improve gingivitis (62). Gingivitis is one of the appropriate reactions to bacterial progress, but it can onslaught to the periodontal condition, in soft bone and tissues which are ruined. Numerous patients have some mild demonstration of the periodontal problem, although between 5% to 20% of people with serious disorders progress among dental problems like loss of teeth (63). Destruction of periodontal lesions often arises in the surrounding oral cavity without any correlation. Apparently, because of the deposits of interstitial amyloid and the aggregation of the membrane of the vascular basement, neutrophil emigration is limited. Periodontal ligament destruction is the individual anatomic aspect of periodontal diseases. In addition, some factors, such as reduction of epithelial adhesion or downregulating epithelial embryonic root proliferation, straight invasion of bacteria, and host or microorganisms' enzyme function. The paradigm of resorption in hard and soft tissues is significantly correlated to pocket forms and caught remarkable irritant gram-negative anaerobic bacterial plaque versus the remnant lesions, undertaking the process of chronic inflammatory phase that remains for years. Furthermore, abundant species of bacteria attached to microbial flora of periodontal despite *Aggegatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis* play major roles in periodontal diseases as abovementioned (18). Normally, gingivitis is correlated with fluctuations of endogenous hormones, plaque, systemic disorders, medications, malnutrition, and a wide range of important features (64). Moreover, some approaches can improve the management of gingivitis induced by plaque, such as routine dental prophylaxis using different oral hygiene production. Many findings have reported that the practice of suitable oral hygiene, containing brushing, and utilizing good mouth rinse can attenuate gingivitis (65).

Current antibiotics treatment in oral infections

Dentists always suggest antibiotics or sufficient drugs to control several oral diseases, particularly orofacial and dental infections. Generally, orofacial infections are characterized by odontogenetic infections that encourage dentists to prescribe antibiotics as the main features of dental practice. Thus, antibiotics usually have been taken on large scales of prescribed medicines (66). Selecting antibiotics requires microbiological analysis, which is attained from samples of impacted areas clinically. Also, choosing appropriate antibiotics is highly associated with clinical signs, the type of pathogen, and even the sensitivity of patients (67). Various antibiotics, such as tetracyclines, metronidazole, clindamycin, fluoroquinolones, etc. are often used as systemic antibiotics in periodontal diseases, which are administered as monotherapy (21). Antibiotic resistance of bacteria in the mouth is steadily increasing, especially *Prevotella* and *Porphyromonas*, and the number of sensitive strains reduced significantly, which is elucidated in recent reports. Despite this, some studies have shown that penicillin, clindamycin, and macrolides affected *Streptococcus viridans* as an important pathogen in oral conditions (68). However, the resistance of bacteria found in periodontal disease has been detected against entire beta-lactam antibiotics involving derivatives of penicillin and cephalosporins, ciprofloxacin, macrolides, and tetracyclines (69). Generally, the most common antibiotics in dentistry that are safe for children and almost for pregnant women are classified in figure 4 (70).

Tetracyclines

Tetracyclines are one of the categories of bacteriosta-

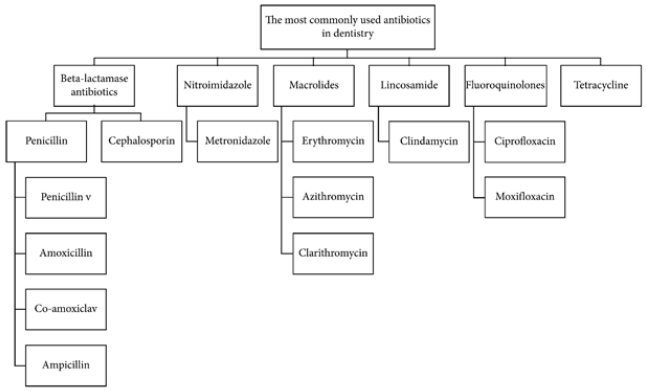

Figure 4. Classification of most commonly used antibiotics in the prevention and treatment of dental and periodontal diseases (70).

tic antibiotics that prepare a "broad spectrum" of action against both gram-negative and gram-positive species, though more appropriate antibiotics are commonly preferable for infections related to Gram-positive. Also, tetracyclines containing minocycline and doxycycline are effective against the main pathogens of periodontal diseases (such as *A. actinomycetemcomitans*) (71). Tetracyclines are also used as the first line of the therapeutic approaches in curing infections, particularly in the treatment of oral infections, resulting from *chlamydiae*, *rickettsia*, *Mycoplasma pneumoniae*, and some types of *spirochaetes* (72). Tetracyclines generally utilize in different routes of administration in oral conditions. For instance, both oral and topical applications of tetracyclines in the therapeutic paradigm of periodontal infections and in the management of teeth that are avulsed (73). Currently, studies have shown that tetracyclines are conducted as sufficient collagenase inhibitors (a matrix metalloproteinases or MMP subgroup) with significant functions in dentistry and oral conditions (74). Absorption of tetracyclines begins from the gastrointestinal tract and decreases when medications are administered with milk products or supplement compounds such as magnesium, iron, aluminum, or calcium. Nevertheless, taken drugs effect even on an empty stomach, and a particular concentration of the antibiotic exist in the bowels (75). All tetracycline antibiotics are localized in progressive dental bone and structure also are distributed widely in the tissues. Doxycycline, minocycline, tetracycline, etc., are recognizable in biological fluids after oral administration, and their certain amounts may reach levels more than ten times in crevicular fluid and five times in the serum, respectively (76).

Metronidazole

Metronidazole has been initially applied to cure infection triggered by *Trichomonas vaginalis* in the 1950s. Afterward, new approaches were found. Recently, Metronidazole has been administered to treat different types of infections, such as dental and oral infections, joint and bone infections, endocarditis, gynecologic infections, respiratory tract infections, and septicemia, which are caused by various bacterial pathogens (*Fusobacteria*, *Clostridia*, and *Bacteroides*) (77, 78). This antibiotic is also used in periodontal treatment with topical application or tablet forms that are more frequent. The drug has good absorption after oral application. Plasma level is usually reached to peak in an hour (79). Metronidazole half-time is around 8 hours and the main organ for the metabolism of the drug is the liver. The distribution of metronidazole provides a considerable concentration of drugs in the body, particularly biological fluids such as saliva or crevicular. Besides, excretion occurred in the urine (80). The principal metronidazole administration in treating periodontal diseases and other dental infections has concentrated on the certainty of drugs for anaerobes microorganisms and manifest susceptible inability of organisms to progress resistance (81). Metronidazole applications have increased in populations. However, some side effects, such as genotoxicity and neurotoxicity, are crucially associated with the use of metronidazole (78). Generally, metronidazole has commonly known to have effective roles in combination with amoxicillin, which has eliminated *A. actinomycetemcomitans* in patients with oral infections. Almost the entire elimination of accumulated biofilms about a year after treatment. Moreover, Guerrero et al. have shown that the systemic usage of amoxicillin and metronidazole and nonsurgical therapy of progressive periodontitis remarkably improved clinical results in 6 months (82).

Clindamycin

Clindamycin has been found to have a wide range of preferred functions against anaerobic infections. The antibacterial range of clindamycin concludes with Gram-negative and –positive anaerobes, Gram-positive cocci, and specific protozoa (83). Also, clindamycin is categorized as bacteriostatic, but it can present bactericidal effects when it is reached at certain doses. Moreover, this antibiotic conducts its mechanism of action by protein synthesis inhibition affecting, particularly, the bacterial ribosome 50S subunit. Synthesis of proteins is initially inhibited in the elongation of the early chain by interfering with the reaction of transpeptidation. (84). Therapy of bacterial infection with adjunctive antibacterials needs suitable antimicrobial amounts to be achieved at infection sites. Despite this, the concentrations of serum are not generally the same as the tissue amount (85). The systemic application of clindamycin reveals to promote high amounts inside the mandibular bone, although the concentration of clindamycin in alveolar serum is approximately 3 times more than the amounts in mandibular bone. In addition, this concentration exceeds the minimum concentration of most bacteria isolated from osteitis syndrome (86). Clindamycin usage has been restricted because of the potential adverse reaction intensity that attends to the administration of this drug. Microbiological, clinical, and short-term experiments have demonstrated that clindamycin is an effective factor in the management of advanced periodontal infections and the treatment of refractory periodontitis (67, 87).

Other antibiotics

Other groups of antibiotics are used in different oral infections, such as PI, periodontitis, gingivitis, etc. One of the most important classes of antibiotics is Beta-lactam antibiotics which include a beta-lactam ring in their chemical structure (beta-lactam ring contains one-nitrogen cyclic amine and a three-carbon structure). These antimicrobial agents have bactericidal effects that oppose abundant anaerobic, Gram-negative, and Gram-positive bacteria by hindering cell wall synthesis (88). Beta-lactam antibiotics are classified into five categories: monobactams, carbapenems, penems, cephalosporins, and penicil-

lin (89). The misuse and overuse of cephalosporins and penicillin caused an increment of bacterial resistance, leading to beta-lactamase production. Furthermore, the resistance risk could be increased if the penicillin group is used together with other groups of antibiotics, for example, metronidazole (20). Allergic reactions containing rashes, pruritis, and anaphylactic shock are among the common adverse reactions of beta-lactams led by immunoglobulin E mediators release (90). Another group of wide-range bactericidal antibiotics is fluoroquinolones which oppose Gram-positive aerobic cocci, Gram-negative bacilli, and anaerobic organisms by inhibiting DNA synthesis (91). Commonly, fluoroquinolones are suggested for nonodontogenic infections, such as bone and joint infections, respiratory infections, and genitourinary tract conditions. These factors have a suitable potential to penetrate into tissues compared to other frequently prescribed antimicrobial agents in dentistry (70). Side effects of fluoroquinolones contain cartilage, tendon, and CNS (central nervous system) involvements and gastrointestinal reactions (92). Also, antibiotics of this group might not be prescribed for childhood patients due to chondrotoxicity possibility in progressive cartilage and for patients who are administered theophylline that can present serious conditions such as seizure (93).

Mechanisms of resistance to different classes of Antibiotics

The bacteria utilize various methods to acquire resistance to aminoglycosides, including aminoglycoside modifying enzymes that cause aminoglycosides to be inactivated, ribosomal mutations, or ribosomal methyltransferase enzymes that cause aminoglycosides to be inactivated, ribosomal modification (94). There are three possible enzyme mechanisms contributing to the development of resistance to macrolides. These processes include the expression of the ereA or ereB gene expression in erythromycin, which hydrolyzes the antibiotic structure, resulting in ecstatic ring cleavage, the mgt gene that leads to glycosylation macrolides, and mphA, mphB, and mphB genes, which result in modification of the 23S rRNA (95). E.coli develops erythromycin resistance due to a sequence mutation altering the II and V domains. Methylation of the A2058 in domain V of other organisms, such as S. aureus, occurs by either adenine N methyltransferase activity or by mutation of A2058 to guanine, resulting in both of which is a reduction in affinity. Fluoroquinolones are resistant to two main mechanisms: alterations in enzymes and alterations in drug-access mechanisms. The DNA gyrase enzyme mutates either in the presence of GyrA, which can cluster into the Quinolone resistance domain (QRDR), thereby reducing the drug's affinity or in the presence of GyrB subunits tend to cluster in a similar QRDR region as well (96). A drug-access alteration occurs when the efflux pumps for multi-drug resistance (MDR) are enhanced, excreting the drug outside of cells before reaching the targeted site. In consequence, a decrease in fluoroquinolone activity has been observed. Moreover, the outer membrane of gram-negative bacteria provides more excellent resistance due to the absence of protein porins, which leads to a lower level of drug diffusion (97). It is thought that bacteria develop resistance to rifampin by acquiring mutations in the rpoB gene, which affect the β subunit of the RNA polymerase, the main target of this antibiotic. Patients who used Rifampin as the only active antibiotic developed resistance to many bacteria, including M. tuberculosis. Therefore, it is recommended to use it in combination with other antibiotics to avoid the development of resistance (98). A mutation in a single amino acid (Phe98 to Tyr98) in the dhfr gene results in trimethoprim resistance in S. aureus and S. pneumonia, resulting in a chromosomal change causing dhfr chromosomal alteration. S. pneumonia is susceptible to sulphonamides due to a duplication of 2 amino acids in the folP gene (dhps gene) that alters the enzyme's tertiary structure (99).

Current drug delivery systems

Recent, local administration of drugs to treat periodontitis has rapidly expanded in drug delivery systems because of straight attachment to the sites of diseases and reducing drug systemic adverse reactions. Several local delivery systems of drugs, such as implants/inserts, particulate formulations (microparticles and nanoparticles), films, and gels, have been examined. They are now available in the pharmaceutical industry (Figure 5). For instance, some local drug delivery systems, such as formulations based on mucoadhesive gel, especially hydrogels, have drawn major attention to periodontitis treatment (100). The current antibiotic delivery systems in different dental infections are listed in Table 1.

Microspheres

Microspheres are used as carriers of active ingredients in local delivery systems in the periodontal pocket. One of the sensitive lesions is inflamed periodontium. Also, local administration of delivery systems can decrease the pain and trauma of patients and might be preserved for the required duration in the pocket. Microspheres have drawn major attention as delivery carriers for DNA, enzymes, antigens, and drugs, particularly as sustained or controlled delivery systems of active substances using biomaterials or biopolymers (128). For instance, chitosan microspheres have been commonly used as carriers of drug delivery systems that are provided through different procedures, such as single emulsion technique, multiple emulsion technique, chemical and thermal cross-linking, and other methods. They have been conducted as a promising application in the formulation of dental paste or even can be injected into the periodontal cavity directly. Furthermore, chitosan microspheres are employed in antibiotics such as doxycycline, tetracycline, ofloxacin, and natamycin have been investigated (129).

Microparticles

Examples of these systems include solid polymeric particles, most notable spheres with a diameter between 1 and 1000 micrometers, encapsulated in a solution with the drug dispersed evenly throughout their volume. A bioactive agent loaded into a polymeric matrix may form physical or

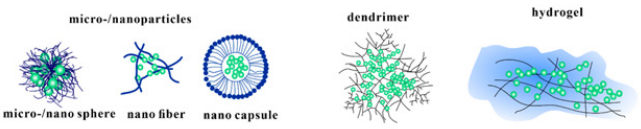

Figure 5. Examples of proper carrier forms of local drug delivery systems (101).

Table 1. Antibiotics delivery systems in different dental infections.

Antibiotic	Type of infection	Study design	Delivery system	Method	Outcome	Ref/Year
Tetracycline	Periodontitis	In vitro	Nanoparticles	Evaluation of release and content of tetracycline in MCM-41 (Mobile crystalline material 41), as a type of MSN (Mesoporous silica nanoparticles), with loaded tetracycline for controlled release of drug	The effectiveness of the tetracycline-MCM-41 nanoparticles was better than free tetracycline against *Escherichia coli* (*E. Coli*), while blank nanoparticles had no effect.	(102)/2015
Meropenem	Nosocomial infections	In vitro	Nanoparticles	Investigation of antimicrobial effects, cytotoxicity, and biocompatibility of meropenem-loaded MSN	Meropenem-loaded MSN has shown low cytotoxicity, proper biocompatibility, and the enhanced antibacterial activity	(103)/2020
Ciprofloxacin	Root canal infection	In vitro	Nanoparticles	Investigation of antibiofilm and antibacterial effects of Ciprofloxacin loaded PLGA nanoparticles coated with chitosan	Ciprofloxacin-loaded PLGA nanoparticles coated with chitosan have shown superior antibacterial and antibiofilm effects in a controlled release procedure than vehicle group	(104)/2020
Gatifloxacine	MO	In vitro & In vivo	Microparticles	Evaluation of release and bactericidal effect of gatifloxacin-loaded PLGA against *Bacteroides fragilis* and *Streptococcus milleri*	Gatifloxacin-loaded PLGA and β-TPC (β-tricalcium phosphate composite) was useful for the local therapy of osteomyelitis and remarkably removed bacteria	(105)/2011
Gatifloxacine	MO	In vitro & In vivo	Microparticles	Investigation of the effectiveness of gatifloxacin-loaded PLGA and hydroxyapatite composite for treating osteomyelitis	Gatifloxacin-loaded PLGA and hydroxyapatite composite controls bacterial infection and supports the regeneration of bone for osteomyelitis therapy.	(106)/2017
Minocycline	PI	In vivo	Microsphere	Assessment of local treatment of PI with minocycline microspheres in 57 implant cases the following debridement	The adjunctive administration of minocycline microspheres is effective in the treatment of peri-implant tissues, although treatment should have be repeated	(107)/2008
Doxycycline	PI	In vivo	Microparticles	Evaluation of doxycycline sustain release. In the 28 patients who had a total of 48 peri-implant defects	Using doxycycline sustained release exhibited a remarkable effect in mean probing attachment Levels and a substantial decrease in depths of pocket probing.	(108)/2004
Doxycycline	PI	In vitro	Gel	Investigation of controlled liberation gel with 14% doxycycline for machined and sandblasted decontamination acid-etched implant	Adjunctive local administration of delivered 14% doxycycline gel would be a proper option in the PI management and peri-implant mucositis, considering its influence on decreasing biofilms	(109)/2018
Clindamycin	Periodontitis	In vivo	Gel	Investigation of gel with1% clindamycin hydrochloride on the microbial flora of periodontal pockets	Application of clindamycin gel inserted in a periodontal pocket has significant effects on periodontitis treatment through remove more microbial colonization	(110)/1993
Metronidazole	Periodontitis	In vivo	Gel	Assessment of metronidazole in the treatment of localized Periodontitis in adults.	The local dental gel of metronidazole improves mechanical characteristics in adult periodontitis as an alternative treatment.	(111)/1999
Doxycycline	Periodontitis	In vivo	Nanospheres	Evaluation of clinical features, antimicrobial, and immune activity using 20% doxycycline-loaded PLGA nanospheres as adjunctive therapy in chronic periodontitis of type-2 diabetics patients	Local application of Doxycycline nanospheres can exhibit an adjunctive treatment in periodontal disease therapy in type-2 diabetic cases, reaching additional benefits in the modulation of the local cytokine, decrement of microbes, and clinical parameters, particularly in deep pockets.	(112)/2020

Minocycline	Periodontitis	In vivo	Microspheres	Evaluation of minocycline microspheres plus SRP (scaling and root planning) in 748 patients suffering from moderate to advanced periodontitis	Minocycline microspheres plus SRP are more sufficient than SRP alone in decreasing probing depths in periodontitis cases.	(113)/2001
Minocycline	PI	In vivo	Microspheres	Comparison of the microbiological effect of local delivery of minocycline microspheres and adjunctive photodynamic therapy in patients with PI	Minocycline microspheres has equal efficacy in the decrement of mucosal inflammation in initial PI	(114)/2014
Minocycline	Periodontitis	In vivo	Microspheres	Investigate the effectiveness of minocycline microspheres, locally applied as an adjunct to SRP in smokers suffering from chronic periodontitis.	SRP plus locally delivered minocycline microspheres treatment is better than SRP alone in decreasing pocket depths in cases	(115)/2003
Minocycline	PI	In vivo	Microspheres	Analysis of minocycline microspheres as an adjunct mechanical therapeutic approach of infected sites adjacent to implants of 32 cases	Minocycline microspheres improve conditions of PI tissues, as a local antibiotic, in probing depths	(116)/2006
Doxycycline	Periodontitis	In vitro & In vivo	Microspheres	Evaluation of doxycycline microspheres with SRP in the treatment of periodontal pocket and complex effect on *Porphyromonas gingivalis*	Local doxycycline microspheres delivery significantly Enhanced the treatment results in the treatment of periodontal pocket and decrease *P. Gingivalis* in the pocket.	(117)/2012
Tetracycline	PI	In vitro	Nanofibers	Evaluation of the osteogenic and antimicrobial activity of tetracycline nanofibers	Tetracycline nanofibers might conduct as an antimicrobial modifier of surface and osteogenic stimulator for dental implants	(118)/2017
Metronidazole /amoxicillin	Periodontitis	In vitro & In vivo	Nanofibers	Investigation of amoxicillin and metronidazole-PLGA nanofibers for the treatment of the periodontal disease	The nanofibers can be utilized in periodontitis treatment as controlled-release systems that can increase compliance of patients and reduce times of administration	(119)/2021
Metronidazole	Periodontitis	In vivo	Nanofibers	Assessment of metronidazole nanofibers in chronic periodontitis cases	A combination of SRP + metronidazole nanofibers exhibited more effective results in the treatment of periodontitis.	(120)/2012
Tetracycline	Periodontitis	In vitro	Nanoparticles	Evaluation of features and antimicrobial activity of calcium sulfate-loaded tetracycline as local nanoformulation for treating periodontitis	Tetracycline nanoparticles improve the locally deliver of antibiotics to the infected areas	(121)/2014
Tetracycline	Periodontitis	In vitro	Nanoparticles	Investigation of regenerative capacity and antibacterial properties of tetracycline nanoparticles for periodontal diseases treatment	Tetracycline nanoparticles revealed suitable antibacterial properties against *E. Coli* and *S. Aureus* bacteria and have the bone regenerative potential for local periodontal use.	(122)/2014
Minocycline	Periodontitis	In vitro	Nanoparticles/ Hydrogel	Evaluation of hydrogel containing minocycline nanoparticles, zinc oxide, and albumin in the treatment of periodontitis	This formulation has proper adhesion to mucosal tissues and effective antibacterial capacity in the treatment of periodontitis	(123)/2019
Doxycycline	PI	In vivo	Nanospheres	Evaluate the combination of doxycycline nanospheres controlled liberation and nonsurgical debridement in the peri-implant defects	Increase clinical parameters betterment in PI	(124)/2012
Metronidazole	Periodontitis	In vitro	Films	Investigation of metronidazole content on the growth of cells, antibacterial effects and release profile of metronidazole films	Suitable biocompatibility and antibacterial properties against the growth of *Bacteroides fragilis* and also proper in periodontitis treatment	(125)/2009
Surfactin	Periodontitis	In vitro	Hydrogel	Evaluation of anti-inflammatory and antimicrobial characterization of hydrogels composed of Sufactin and nanofiber carrier in the treatment of periodontitis	The hydrogel has antibacterial and anti-inflammatory characterization in periodontitis treatment	(126)/2020
Doxycycline	Periodontitis	In vitro	Nanoparticles	Investigate the doxycycline nanoparticles containing chitosan on peridontitis	Increase clinical parameter improvements and exhibit novel mechanisms to prove local delivery systems of antibiotics in periodontal diseases	(127)/2020

chemical bonds with the matrix, or the drug may be merely adsorbable on its surface. Both natural and synthetic polymers are used to make these powdery materials. For this purpose, some polymers can be used, including those that are biodegradable (PLGA, polylactide, and poly(hydroxy alkanoates)) and those that are polysaccharides (CS, pectin, hyaluronic acid, etc.). As part of the process of obtaining microparticles, several techniques are involved, including emulsification, solvent evaporation, coacervation, spray drying, and electrospray. Directly into periodontal pockets or with toothpaste, suspensions, or toothpaste, suspensions can be administered. As a result of using such systems, you can benefit from several benefits, including controlled release, higher patient compliance, and a more sustained therapeutic effect due to the controlled release of the medication (130-132). As part of the study, an antimicrobial decapeptide, KSL-W (KKVVFWVKFK-CONH2), was added to PLGA/CS composite microspheres prepared by electrospraying and combining cross-linking and emulsion methods, which could maintain stable antimicrobial activity in saliva (Figure 6) (130, 133-135).

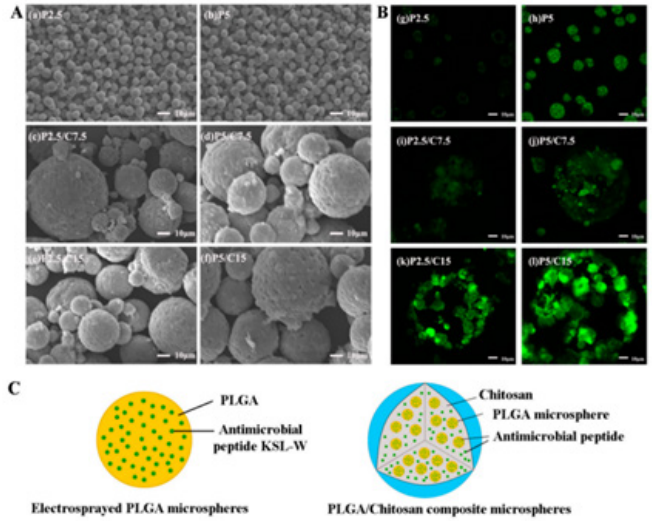

Figure 6. As shown in (A), the KSL-W-loaded PLGA and PLGA/CS composite microspheres were examined by scanning electron microscopy (SEM); as shown in (B), KSL-W FITC conjugates were visualized under a laser scanning confocal microscope (LSCM), while (C) schematic diagrams for PLGA and PLGA/CS microspheres loaded with KSL. PLGA, poly(lactide-co-glycolide); CS, chitosan; FITC, fluorescein isothiocyanate (130).

Nanoparticles

Nanomaterials are generally defined as particles with 10^{-9} to 10^{-7} m that have the potential to use in antimicrobial treatment due to their proper physicochemical characteristics like nanosized, enhanced chemical responses, and large surface area to mass ratio (136, 137). Nanoparticles can prepare novel procedures for the prevention and treatment of oral and dental infections. The high charge density and large surface area of nanoparticles authorize them to contact with bacterial cells negative charge surface to better magnitude consequent in increased antibacterial action. In addition, nanoparticles coupled with coated biomaterial or polymer surfaces were determined to present great antibacterial activity in the oral cavity (138). Damage dental lesions may cause periodontal disease, dental caries, the sensitivity of teeth, bad breath, or oral malignancy. These conditions may be treated by using biocompatible materials and therapeutic approaches. Although there is a lack of precise understanding of dental community features, various types of nanocomposites and nanoparticles have been revealed to imitate host tissues properties (139).

Nanoparticle in Restorative dentistry

Dental caries, caused by bacteria living in the oral cavity and usually repaired with materials similar in color to the teeth, is an infectious disease that often occurs in the oral cavity. However, restoration failure or secondary caries can occur if antibacterial properties are lacking or microbes and microbial acid production cause demineralization (140-142). Many researchers have become interested in nanotechnology as a result of its development. Dental caries can be prevented using two different methods. First, inorganic antimicrobial NPs can be incorporated into resin composites and ingredients to reduce microorganism biofilms by direct contact. It was found that composite resins containing silver nanoparticles (AgNPs) or zinc oxide nanoparticles (ZnO NPs) showed better antibacterial activity when they contained 1% of those NPs. It is noteworthy that composite resins containing ZnO NPs had a significantly more antibacterial effect on Streptococcus mutans (S. mutans) than composite resins containing AgNPs. Moreover, AgNPs formed in situ through a photoreduction mechanism concomitant to the polymerization process were able to inhibit the activity of S. mutans significantly (132, 143, 144).

There were no adverse effects on the antimicrobial properties of dental resins, even when the nanofillers were at a low concentration. Some researchers have noted that resin cement with the addition of AgNPs, and dental sealants that were modified with nylon-6 and chitosan nanofibers were not able to demonstrate any antibacterial activity against S. mutans in their studies (145, 146). With near-infrared radiation, graphite oxide, AgNPs, and phthalocyanine molecules cooperated to achieve long-lasting disinfection. Additionally, colloidal metal oxide NPs were demonstrated to have superior antibacterial properties. Secondary caries have been prevented and reduced using glass ionomer cement (GICs) that release fluoride ions (147, 148). In addition to improving antibacterial properties, copper-doped glass ionomer-based materials contributed to collagen degradation reduction (149, 150). A significant improvement in mechanical and antibacterial properties was achieved by adding titanium dioxide (TiO2) NPs (151). As a result of the incorporation of hexametaphosphate nanoparticles into GICs, antibacterial properties were effectively enhanced as well as fluoride ion release. It should be noted, however, that ZnO NPs added to GICs did not enhance the antimicrobial activity against S. mutans. An organic NP is used as a second methodology for decreasing demineralization and achieving remineralization. Several combinations of amorphous calcium phosphate nanoparticles (NACP) with polymerizable quaternary ammonium methacrylates (QAMs), such as quaternary ammonium polyethyleneimines (QPEI), quaternary ammonium dimethacrylates (QADMs), dimethylaminohexadecyl methacrylates (DMAHDM), and organic antibacterial NPs have been studied. QPEI NPs were incorporated into modified composites that demonstrated excellent antibacterial activity and durability over long periods. QADM and AgNPs in a composite exhibit a

more potent antibacterial effect that can last for 12 months following water aging (138). Microcosm biofilms did not exhibit a significant amount of metabolic activity or colony-forming units (CFU) when bonded with antibacterial bonding agents containing DMADDM and AgNPs, even when the dental adhesive was pre-coated with salivary pellicles. DMAHDM, 2-methacryloyloxyethylphosphorylcholine (MPC), and NACP have also been studied in combination. In recent years, MPC, one of the most common biocompatible and hydrophilic biomedical polymers, has been used in dental bonding agents and composites as a consequence of its hydrophilicity, which prevents proteins from adhering to it (152). Combining NACP with resin composites can release high levels of calcium and phosphorus ions, neutralize acids, and inhibit dental caries due to its mechanical properties. For long-term caries prevention, a rechargeable NACP composite has been developed with multiple release capabilities (153, 154). The methodologies for applying NACP, MPC, and DMAHDM can be applied to other restorative dental composites, adhesives, and cement to reduce plaque biofilm formation. According to Noronha et al. (2017), recent advances have been made in studying the mechanism of action and essential aspects of toxicology. It was found that several in vitro studies have shown that AgNPs when used in conjunction with dental materials such as nanocomposites, acrylic resins, resin co-monomers, adhesives, intracanal medications, and implant coatings, demonstrated excellent antimicrobial activity. The antitumor properties of AgNPs have also proven helpful in treating oral cancers (155). PLGA NPs loaded with CHX have been fabricated in micron-sized dentinal tubules of demineralized dentin substances and at resin-dentin interfaces by Priyadarshini et al. (2017). Physicochemical properties of the formulated NPs were favorable, low cytotoxicity was low, potent antibacterial activity was demonstrated, and the CHX release profiles were gradual and slow. In a simulated upward pulpal hydrostatic-pressure path, NPs are delivered efficiently and at sufficient depth inside dentinal tubules. Although bonding resins infiltrate the dentin, they have been attached to collagen fibrils and retained there. It also promotes a new era of dental research for future clinical applications utilizing this newly introduced drug-delivery therapeutic strategy. The effectiveness of this innovative drug delivery strategy has been demonstrated over time and is expected to be extended to other areas of adhesive and restorative dentistry (154, 156, 157).

Nanoparticles in root canal therapy

A long-term periodontal disease, known as secondary dental caries, is caused by bacteria and their products and can result in pulpitis and apical periodontitis. After root canal therapy, reinfections are primarily caused by Enterococcus faecalis (*E. faecalis*). It is complicated to complete microbial cleanup after root canal preparation and filling (158, 159). Biosynthesized AgNPs had antibacterial properties against *E. faecalis*. In comparison to NaOCl, poly (vinyl alcohol)-coated AgNPs (AgNPs-PVA) and farnesol (FAR) was significantly more effective in repairing tissue, as well as being less cytotoxic (160). The effectiveness of nano-MgO (5 mg/L) and nano-chitosan NPs in eliminating *E. faecalis* in the root canal system was statistically significant when compared to 5.25% NaOCl (161). An earlier study showed that biomimetic iron oxide NPs with a peroxidase-like activity could enhance the antibacterial activity of root canal surfaces and dentinal tubules in a healthy human mouth. The antibacterial properties of NPs may be affected by their form. With CHX-AgNPs containing lyotropic liquid crystals (LLCs), there was excellent and sustained sterilization and a 98.5 percent bacterial inactivation rate when *E. faecalis* was exposed, lasting more than a month. Additionally, cytotoxicity evaluations did not reveal any toxicity (162). Recent publications show that AgNPs irrigants were less effective than NaOCl against *E faecalis* biofilm and infected dentinal tubules. This was consistent with the conclusion that AgNPs gel was more effective as an irrigant than the solution. Furthermore, NaOCl is the most effective irrigating solution for root canal treatments (163). Antibacterial materials should be developed for root fillings in endodontic treatment to prevent secondary infections. A paste containing 0.15% AgNPs and 2.5% DMAHDM exhibited significantly higher antibacterial activity against *E. faecalis* than a paste without nano-fillers (164). There is no doubt that calcium hydroxide (Ca(OH)2) is one of the most commonly used intracanal medicaments in clinical practice. An increase in the antibacterial activity of Ca(OH)2-based paste may be achieved by incorporating chitosan NPs (165). In both Ca(OH)2 and chitosan nanoforms, superior penetration into the dentinal tubules and significant antibacterial activity were demonstrated. The addition of NPs promoted antibacterial activity in Ca(OH)2 and other filling materials (166). By mixing calcium silicate cement with varying concentrations of AgNPs, they showed significant enhancements in their antimicrobial activities. Mineral trioxide aggregate and Portland cement both showed antimicrobial effects. A similar reduction in bacteria viability and a promotion of cell death was also observed with the addition of QPEI NPs (167). A new type of mesoporous chitosan (MesoCS) NP has been developed by Huang et al. and is capable of osteogenesis, drug delivery, and antibacterial properties for endodontic materials and is able to mineralize apatite. A facile template method was used to synthesize 200-nm-sized MesoCS NPs, which displayed high specific surface area and pore volume, as well as internal mesopores. As a result, MesoCS NPs can be used as drug carriers that can maintain sustained releases of drugs such as gentamicin and fibroblast growth factor-2 (FGF-2) for a more extended period. MesoCS-loaded FGF-2 may stimulate more odontogenic-related proteins than chitosan since FGF-2 is released when MesoCS is inserted into the ear (168).

Upon attachment and penetration of nanoparticles into bacterial cell walls, Gram-positive and Gram-negative bacteria are disrupted by the release of ions related to the attachment and penetration (36). Therefore, NPs are advantageous for preventing and treating diseases caused by drug-resistant microorganisms and inhibiting biofilm formation. The antibacterial mechanism of NPs can be roughly divided into three types, although the specific mechanism of action is not yet precise. There are three antibacterial mechanisms described by the authors: (1) interactions with peptidoglycan cell walls and membranes and the resulting cell lysis; (2) interactions with bacterial proteins and disruption of protein synthesis; (3) interactions with bacterial DNA (cytoplasmic) and the prevention of DNA replication (17, 169). As the representative of inorganic NPs, AgNPs have been reported to interact

with the abovementioned structures to inhibit respiratory chain enzymes and interfere with membrane permeability. Through AgNPs' catalytic action, oxygen could be converted into active oxygen, causing microorganisms to become structurally damaged, which is known as Ag's "oligodynamic action" (170). The second most abundant natural polymer after chitin, chitosan represents organic NPs. The antimicrobial properties of chitosan are broad and include biocompatibility and biodegradability (171). The antibacterial mechanisms of chitosan NPs are similar to those of Ag NPs. There are limitations for the use of NPs despite their significant antibacterial activity. These limitations include varying concentrations of antibacterials against micro-biofilms, toxicity, and potentially adverse effects on human health.

Films

Films are one of the acceptable dosage forms for patients during the treatment of periodontitis. Periodontal pocket anatomy prepares a proper application for the simple insertion of films with suitable sizes. Alginate, chitosan, cellulose, and gelatin-originated polymers such as sodium carboxymethyl cellulose, hydroxyl propyl methylcellulose, and ethylcellulose throughout degradable biomaterials have been frequently used as films for medical use and medical experiments (172). The efficacy of periodontitis therapeutic approaches is related to the capacity of the release system to increase the duration of drug release. To control the rate of drug release, cross-linking has an important position in techniques of forming films. For instance, complexes of polyelectrolyte are macromolecular forms containing repetitive units and are structured by a network among nucleic acids, proteins, and oppositely charged polymeric particles in each ionizing solvent, such as ethanol or water (173). The shape and dimensions of films are usually controlled following the pocket dimensions to be cured. One of the advantages of films is quick insertion into the periodontal pocket base with the least pain and distress to the patients (174). Findings revealed that films with thicknesses lower than 400 μm and adequate adhesion would keep submerged without discernible disruption of oral hygiene habits in patients. Films release antibiotics by alone diffusion interference to non-degradable polymers, which are insoluble in water, whereas films releasing antibiotics through matrix erosion, diffusion, and dissolution use biodegradable or soluble polymers (175). Opposed to systems with non-degradable polymers, the films are provided with dissolved or eroded degradable polymers in the gingival crevice. Therefore, elimination after therapy is not necessary (176).

Hydrogels

The term hydrogel refers to a derived form of a gel that consists of hydrophilic polymer chains that are crosslinked to create a three-dimensional solid. In general, two different types of crosslinking methods are used to bind the polymers of a hydrogel: chemical and physical. As opposed to gels that can be diluted and disintegrated, hydrogels can absorb a significant amount of water (over 90%, in some cases with a capacity of over 10,000%) without disintegrating or fluidizing. Hydrogels possess physicochemical properties that are similar to those of native extracellular matrices in part due to their ability to incorporate large amounts of water and substances dissolved in them (130). Using the functional groups -OH, -NH2, and -COOH of polysaccharides, chemical cross-linking will create three-dimensional structures from bifunctional compounds (dialdehydes, epichlorohydrin). Alternatively, the polysaccharide can be functionalized with polymerizable groups, so a chemical, thermal, or photochemical polymerization process can form the hydrogel network. It is possible to obtain hydrogels by double cross-linking, by which covalent cross-linking is partially replaced by ionic cross-linking. So, the toxicity of the product is reduced. To ensure a minimum level of structural and mechanical stability, a minimum amount of covalent cross-linker must be maintained (130).

Gels

Gels are known as one of the various drug delivery systems such as films, ointments, implants, or films, which are utilized in nondegradable or biodegradable polymers that have been examined for the treatment of periodontal diseases. Among these carriers, formulations based on mucoadhesive gel have drawn major attention in periodontitis therapy. Commonly, the preparation of gel-based is classified into two major groups based on external liquid phase polarity (177). In organogels/oleogels the external liquid phase is oil, and the external liquid phase of hydrogels is water or an ionizing solvent. Moreover, hydrogels are prepared by the three-dimensional system of synthetic or natural gelling agents to paralyze the aqueous phase (178). These systems provide better compliance of patients due to their certain traits such as cooling effect, simple elimination after utilizing, ungreased texture, and proper capacity of spreading. Hydrogels show great biocompatibility and mucoadhesive characteristics, as they are linked to the mucosa in dental pockets and decrease irritation at application areas. An important disadvantage of the hydrogel-based formulation is that they can be insufficient carriers for drugs with lipophilic structures (179). Oleogels/organogels are settled as semi-solid preparing obtained through lipophilic liquids gelation with the utilization of the proper compound entitled organogelators. The forms of gelling agents accumulate and connection between accumulates, which give rise to the three-dimensional systems formation (180). Organogels/oleogels have desirable rheological features that guarantee superior solubility of hydrophobic substances. Also, because of the water absence, they are impervious to contamination by microbes, and the addition of preservatives is not required. Furthermore, utilizing lipid vehicles can supply prolonged release, cover their disagreeable taste, and protect active compounds from degradation in hydrophilic conditions in the treatment of periodontal diseases (100). Many hydrogels and oleogels for the delivery of metronidazole (25%), tetracycline (2.5%), metronidazole benzoate (40%), along with a combination of metronidazole benzoate (40%), and tetracycline (2.5%), have been studied and positive outcomes have been obtained. Mucoad hesion and bioadhesion is an initial necessity for the prolonged liberation of antibiotics at the areas (181). Some kinds of gels are more functional than other gel carriers. For instance, the retention time of chitosan gels is remarkably higher in comparison with polyethylene oxide gels and xanthan gums. Therefore, depending on the aim of drug release, a suitable gel carrier can be chosen. Chitosan in gel form with or without 15% metronidazole has revealed proper efficacy in chronic periodontitis treat-

ment (182). Semi-solid bioadhesives polymeric network may be used as a main intra-pocket delivery carrier due to its simply transported by a cannula into periodontal pockets, where it is solidified in situ to release the drugs or therapeutic factor for an extended period. These combinations show thermo-responsive behavior and pseudo-plastic flow that exists as a liquid at room temperature and gel at 34-37°C (183). Also, new drug delivery systems such as gels, fibers, or films have a broad range of usage in dental problems comorbidity with diabetes or smoking that can be administered locally in periodontal pockets which are shown in figure 7 (101).

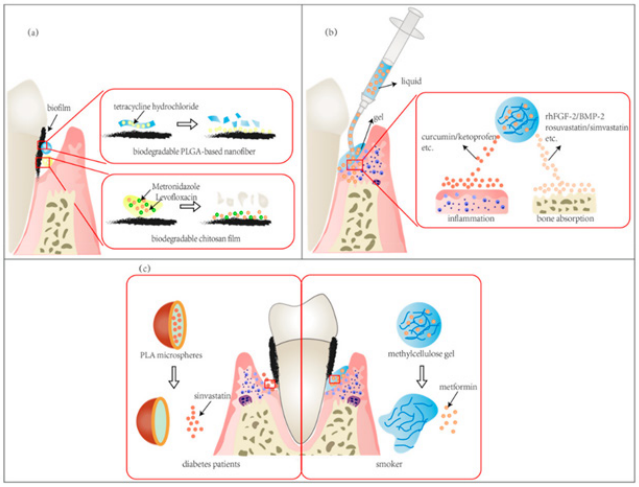

Figure 7. Drug delivery systems application in periodontitis. (a) Drug delivery system containing antibiotics such as metronidazole, and levofloxacin in carriers of antibiotics like films and fibers. (b) Injectable drug delivery systems are usually used for the reduction of inflammation, repair of alveolar bone and immunomodulation. (c) utilization of drug delivery systems in periodontitis comorbidity with diabetes or smoking (101).

Dextran

In the presence of sucrose, the bacteria in lactic acid bacteria or their enzymes can synthesize extra, a complex branched polysaccharide. Glucose molecules are linked by α-(1→6) bonds, with possible branches of α-(1→4), α-(1→3), or α-(1→2) bonds linking D-glucoses together. The physico-chemical properties of dextran and its physiological acceptance have made it an attractive candidate for delivering a wide variety of therapeutic agents. Microparticles containing interleukin 1 receptor antagonist (IL-1ra) have been prepared using dextran in combination with poly-(lactic-co-glycolic acid). A comparison of the results from the present study showed that microspheres developed as a result of the research were excellent candidates for the treatment of periodontitis, as they effectively inhibited the expression of pro-inflammatory factors induced by IL-1β in human gingival fibroblasts. Several studies have indicated that dextran may be an appropriate microcarrier for gene delivery to patients undergoing dental implant treatment to restore their oral health. Organic solvents may become a critical issue, especially in pediatric dentistry, as organic solvents may have toxic effects on polymer micro- and NPs (184). As a result, it is crucial to avoid such solvents during the preparation of particle structures, such as the human bone morphogenetic protein (BMP), to prevent possible damage and loss of bioactivity during this process. In response to these arguments, a microcarrier based on dextran for the delivery of rhBMP2 was developed. Further studies have been conducted on the potential use of dextran nanoparticles as alternatives to the microcarriers described above. To deliver growth factors to periodontal regeneration, composite glycidyl methacrylate dextran (Dex-GMA)/gelatin nanoparticles are small and can be dispersed more effectively and deliver drugs precisely to tissues and cells (184).

Gels based on miscellaneous polysaccharides

The macrosaccharides (gellan) and cellulosic derivatives of bacteria have the benefit of being highly soluble in water, forming gels at higher concentrations, and possessing bioadhesive properties. These macrosaccharides are commonly mixed with synthetic polymers and other macrosaccharides. It is also possible to generate sustained and stable drug releases using this polysaccharides category, especially when mixed with Poloxamer. Poloxamer 407 and methylcellulose are mixed at room temperature to form a thermosensitive gel, which releases simvastatin continuously for ten days after the initial release (130).

Starch

Among the biopolymers that are frequently used in the dental and medical industries is starch, which is another biopolymer utilized in the development of micro- and nanocarriers. A polysaccharide consisting primarily of anhydroglucose units joined by glucosidic bonds, it is a polysaccharide capable of forming microcistrides and hydrocarbides. It contains two different structural components: amylose (α linear structure of glucose units connected by α-1,4) and amylopectin (a branched structure of α-1,4 chains connected by α-1,6). Among its advantages, starch is biodegradable, renewable, and relatively inexpensive. Several drug delivery systems for dentistry have also utilized this technology, although not as widely (184). As many synthetic therapeutic agents are potentially harmful to children's teeth, they are not appropriate for preventing and treating tooth decay and periodontitis in children. Therefore, the use of gentler organic biomolecules is necessary. It has been proposed by Rezapour et al. that curcumin can be used, in conjunction with starch NPs, to decrease dental caries. Natural anti-inflammatory agents such as curcumin (produced by *Curcuma longa* plants) can prevent biofilms and plaque formation by inhibiting the action of S. mutans, which produces biofilms on teeth. In terms of delivering the active substance in the oral cavity, the starch-based nanostructures suggested in this study seemed to be an effective method that overcomes limitations such as curcumin's poor solubility and bioavailability in the oral cavity (184).

Chitosan-based gels

The mucoadhesive properties of Chitosan and its intrinsic antimicrobial properties make it ideal as a drug carrier. Furthermore, Chitosan meets all of the criteria for polymers that can be used as drug carriers. Using chitosan-based gels, tetracycline hydrochloride and metronidazole benzoate can be incorporated and released from different concentrations of solutions. In the local treatment of periodontitis, it has been demonstrated that a 3% concentration of the chitosan solution is optimal, allowing for optimal modulation of the dosage of the drug substance. Triclosan

and flurbiprofen have been used to create chitosan-based nanogels with anti-inflammatory and antimicrobial properties. A nanogel containing flurbiprofen was directly loaded with the drug, and triclosan NPs were prepared using poly(ε-caprolactone) (PCL). There was a sustained and rapid release of drugs in vitro with both systems. The in vivo tests conducted on rats demonstrated that the gels had improved anti-inflammatory properties and reduced bacterial plaque formation (130).

Sodium alginate

Alginates are naturally occurring polysaccharides derived from the cell walls of brown algae. They are water-soluble polysaccharides. This type of copolymer consists of linear links between molecules of D-mannuronic acid (M) and β-(1,4)-linked molecules of L-guluronic acid (G). There are two types of manuronic and guluronic blocks: homogeneous (poly-G, poly-M) and heterogeneous (MG). In addition to being non-toxic, biodegradable, and biocompatible, sodium alginate is a helpful biopolymer for application in the dentist's office because it is also non-toxic, biodegradable, and biocompatible in the oral cavity. The most widely used impression material in dentistry is alginates, which are hydrophilic, elastic, and relatively inexpensive. They may also have the potential as carriers of oral drug delivery, a fact that should not be overlooked. As can be seen in figure 8, there are several ways to prepare alginate particles to be used as drug delivery systems. Among these are alginate-based microbeads that are promising as local chlorhexidine release devices in the treatment of periodontitis (184).

Pectin

In terms of its composition, pectin is a polymer composed of D-galacturonic acid and L-rhamnose, mainly extracted from citrus or apple fruits. As a thickening and gelling agent in food and beverages, it is a non-toxic natural polysaccharide. An obvious contributing factor to tooth decay is enamel erosion caused by acids. This type of erosion is controlled by pectin. A well-established method of preventing dental erosion is to add pectin to acidic soft drinks. Pectin has been shown to possess bioadhesive properties, bind to mucins and mucous membranes, and adsorb to enamel surfaces as a drug carrier. It has been reported that nanostructures or microstructures of pectin can be formulated to encapsulate active substances. Even though this type of polymer particle can be developed in various ways, including emulsion-based methods, coacervation, or spray drying, the most common method for producing micro- and nanostructures is by ionotropic gelation of pectin.

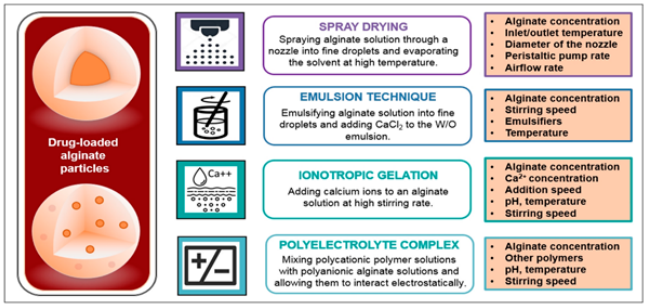

Figure 8. Alginate particles containing drugs and the main formulation methods and process parameters affect their production (184).

The formation of strong ionic bonds between the cations and the galacturonic acid of pectin occurs in the presence of calcium, zinc, or copper ions, as in alginate. When it comes to producing long-acting delivery systems, pectin's rapid swelling in the saliva and dissolution is generally considered to be a disadvantage for the polymer (184).

Fibers

Various polymeric materials can produce electrospun fibers, including biopolymers, synthetics, and a combination of the two. These fibers have a wide variety of applications. They can serve as drug delivery systems (DDS) or cell carrier systems in tissue engineering applications. An applicator generally places these fibers within the periodontal pocket; sometimes, cyanoacrylate adhesive holds them. Encapsulated drugs are released directly into the periodontal pocket, mainly when contained within the lumen fibers. Although these fibers have several advantages, some patients have reported discomfort during placement and slight inflammation of their gums manifested by redness following the insertion of the fibers into the bag. An example of such a system is collagen fibers with tetracycline loaded into them, which have been successfully used to treat chronic periodontitis for three months. In another study, a mixture of glycerin and alginate, crosslinked by ionotropic gelation (in the presence of Ba2+ cations), was packed with ciprofloxacin and sodium diclofenac salts and loaded with ciprofloxacin as well. As a result of this system, microbial cultures of *E.coli*, *E. fecalis*, and *S. mutans* have been inhibited for over 10 days, and it has proven to be a promising drug release system. Gentamicin sulfate was added to other PCL systems. *Staphylococcus epidermidis* was effectively suppressed for two weeks by the system in this instance (130).

Drug delivery system of antibiotics in dental infections

Different therapeutic approaches for periodontal infections have been suggested in analyses. These contain regimens for control plaques, mechanical debridement of infected sites, irrigation with antiseptic factors (such as chlorhexidine and normal saline), laser therapy, and access of surgical flap into PI lesions (185). As it turns out, the bacteria can move from periodontal teeth to implants, and PI-related microbes are similar to periodontal diseases (186). One of the principal procedures for chronic periodontitis treatment includes periodontal pockets mechanical debridement through root planning and scaling as well as sufficient control of plaque to remove bacterial infections (187). Following methods of periodontal regenerative are taking a lot of time and expense, and recently there is no ideal treatment to complete the therapeutic approach of periodontitis and attain the anticipated regeneration of tissues. Due to the periodontitis progression containing a complicated, consecutive association between inflammation, infection, and loss of tissues, therapy could be improved through controlled liberation of multiple bioactive agents in a suitable succession (188). Some therapeutic approaches to periodontal diseases concluded antibiotics localized delivery to remove bacterial infections, while others have deal with inflammation or resorption of bones. Regeneration of periodontal tissue has been conducted utilizing osteogenic factors local delivery. The local delivery of several antibacterial agents in the treatment of chronic periodontitis and their benefits have been examined in the

Etienne et al. study (187). Many antibacterial agents involving tetracycline, doxycycline, minocycline, ciprofloxacin, and metronidazole are used in various oral infections and periodontal diseases (189). Some oral infections, such as MO, require a challenging and long process to treat with long-term antibiotic administration and multiple surgical procedures (190). In general, the antibacterial characteristics of new drug delivery systems can be achieved by inserting agents such as one or more antibiotics into the proper carriers. Bacteria are eliminated by contact with biomaterials as carriers or through antibacterial agents leaching into the body surroundings (191). Arafa et al. found that ciprofloxacin nanoparticle formulation with PLGA (Poly-lactic-co-glycolic acid) and coating it with chitosan were provided, demonstrated a pattern of controlled drug liberation, also coating of particles with cationic chitosan showed effective encapsulation, higher prohibition area, and more antibiofilm impact than an antibiotic or nanoparticles without biomaterials as well as chitosan. In the treatment of infected root canal utilizing chitosan loaded ciprofloxacin as a new antibiotic delivery system with controlled release of antibiotics (104). Also, stimuli-responsive drug delivery systems have proper potential for using in oral diseases therapeutic approaches underlying particular anatomical and physiological features in dental infections that are mentioned in Figure 9 (101).

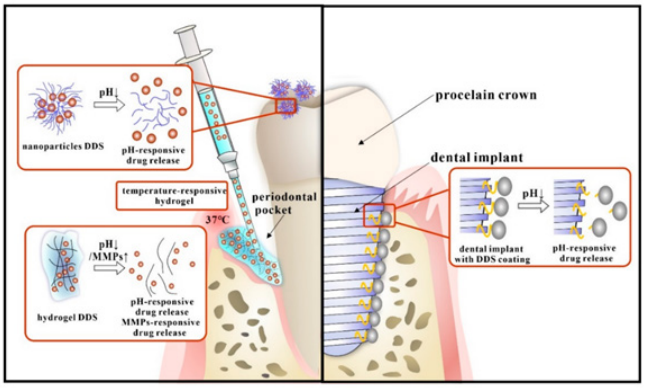

Figure 9. Recent stimuli-responsive drug delivery system in dental infections (101).

Conclusion

Antibiotics such as tetracyclines, metronidazole, lincosamides, and fluoroquinolones are commonly prescribed in dental processes to treat various infections which are related to the oral cavity containing local infection, odontogenic infections, focal infections, nonodontogenic infections, periodontal infections, and prophylaxis. Sometimes antibiotics are used for patients with metabolic disorders, infective endocarditis, immunosuppressed diseases, and patients with prosthetic joints due to prophylaxis of infections. Nevertheless, prescribing antibiotics has complications, concluding bacterial resistance, the appearance of adverse reactions, and effects on tissues that are not aimed at delivering the drug. These complications might be reduced by novel delivery systems, preparing new antibiotics, or new methods. Furthermore, antibiotics are usually used as adjuncts to treat peri-implantitis and stimulate the healing of preimplant tissues that are inflamed and defective. Some mechanical approaches, such as mechanical disinfection and debridement of implants, eliminate the periopathogenic fungal and bacterias and oral biofilms but these pathways are not adequate for specific bacterias and oral biofilms due to the diversity of surfaces features and variation of implant systems morphology. Thus, antibiotics are major parts of peri-implantitis treatments which are utilized locally and systemically. As abovementioned, various antibiotics are usually used in therapeutic approaches or prevention of different dental infections such as PI, gingivitis, periodontitis, and MO. These infections have diverse treatments involving local or systemic utilization of antibiotics which are the most appropriate choice for improving patient health conditions in each type of periodontal, dental, or oral infections. Moreover, the accurate use of antibiotics is crucial for the treatment of dental infections. For instance, Tetracyclines (Doxycycline, Minocycline, Tetracycline) are favorable options as functional antibiotics in peri-implantitis, although the antibiotic resistance of patients plays an important role in approaches of treatments and select individual antibiotics. Also, new findings elucidated that novel drug delivery systems such as films, particulate formulations (nanoparticles, microparticles), and hydrogels enhance the efficacy of drug release and improve the certainty of delivery into the aimed area. The novel delivery systems of antibiotics need biomaterials or biocompatible materials as carriers to transport easily in different situations of biological fluids or tissues. These combinations not only improve efficacy and make individual antibiotic delivery simple but also prevent resistance of specific bacterias against antibiotics.

Prospective in the future

Generally, new drug delivery systems methods will increase efficacy, the bioavailability of antibiotics, and decrease systematic or localized side effects due to the precise transportation of antibiotics into certain tissues, particularly oral, dental, and periodontal areas infected or at high risk of being infected. The administration of new drug delivery systems should be examined in different forms of carriers to find the ideal structure for each antibiotic because of their physicochemical characteristics and proper release. However, using novel antibiotic delivery systems requires more in vitro and in vivo studies to clarify exact information of bioavailability, proper carrier for each antibiotic, toxicity, and efficacy of the combinations to pretend dentists and surgeons suggest using novel methods in periodontal, oral, and dental infections. Also, more clinical examinations can provide details about the compatibility and acceptance of patients in treatment with antibiotics which are carried through nano- and microparticles, gels, fibers, films, and other novel transporters.

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Ethical approval

This article is a review and does not contain any studies with humans or animals performed by any of the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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