SYSTEMATIC REVIEW

Antimicrobial strategies for scaffolds aided periodontal regeneration — road so far. A systematic review

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Abstract

Objective: To give a comprehensive understanding of the efficacy of antimicrobial-loaded scaffolds as drug delivery system for periodontal regeneration, and to review the recent advances in the field of periodontal regeneration.

Methods: The literature was reviewed using key words "antimicrobial releasing periodontal scaffolds" on Science Direct, PubMed and Web of Science search engines. Shortlisted articles were evaluated on the basis of specific inclusion-exclusion criteria.

Results: Of the 544 studies found, 34(6.25%) met the inclusion criteria. The trend indicated an increase in use of antimicrobial-loaded scaffolds that caused inhibition of periodontal pathogenic bacteria, accompanied with greater cellular interaction, and differentiation for alveolar bone healing. Contemporary treatment tactics clinically prove the ability to limit disease progression, but complete periodontal regeneration needs to be validated yet.

Conclusion: Emerging trends are not only improving the inhibitory effect of bacterial growth, but are also making a favourable environment for cell proliferation and differentiation, resulting in alveolar bone repair and re-growth.

Keywords: Periodontal scaffolds, Antimicrobials, Alveolar bone regeneration.

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Introduction

Periodontal disease, also acknowledged as a disease of gingiva, supporting connective tissues and alveolar bone, is an inflammatory condition initially marked by swollen and bleeding soft tissues surrounding the teeth, which, when untreated, progresses into gingival recession, leading to bone resorption and eventually tooth loss.[1] The prevalence of periodontal disease differs in various demographical regions, with Asian countries having a slightly higher rate of incidence and severity. It affects around 2-20% of the adult population with 300 million people being affected worldwide, while in Pakistan a study reported about 98% prevalence rate.[2]

Complete regeneration of periodontal defects remains a challenge. Two major approaches for treatment include conventional approach and innovative new modalities for correcting periodontal defects like, guided tissue regeneration (GTR) and guided bone regeneration (GBR), various grafting materials and enamel matrix derivatives (EMDs). These materials aid in treating periodontitis, but in chronic conditions, these are of little help due to bacterial invasion.[3]

Evidence-based dentistry is attempting to use tissue engineering approach for periodontal regeneration by stem cells, growth factors and using appropriate matrix-based scaffolds. These three-dimensional (3D) biomimetic scaffolds provide an in-vivo environment that allows cell adhesion and proliferation.[3] Biopolymers are preferred due to their low cost, biocompatibility, biodegradability and good mechanical properties.[4]

Electro-spinning (E-spinning) is a method which fabricates scaffolds with fibres of different orientations and pore sizes.[4] Different pore sizes within scaffolds made possible loading drugs and controlled drug release. The antibacterial employed inhibited main periodontal pathogens, including porphyromonas (P.) gingivalis and other oral pathogens.[5]

The main challenge for now is to obtain both mechanical and functional bio-stability along with vascularisation of the in-vitro grown cells. This complex functionality possesses some serious hurdles in this interdisciplinary field.[6] The current systematic review was planned to evaluate different studies involving antimicrobial-loaded periodontal scaffolds and its drug delivery, thereby estimating the clinical validity of the use of antimicrobials within periodontal scaffolds.

Methodology

The systematic review was done at the Army Medical College, National University of Medical Sciences (NUMS), Rawalpindi, Pakistan, in April 2018, and comprised studies published in English language up to April 20, 2018. All

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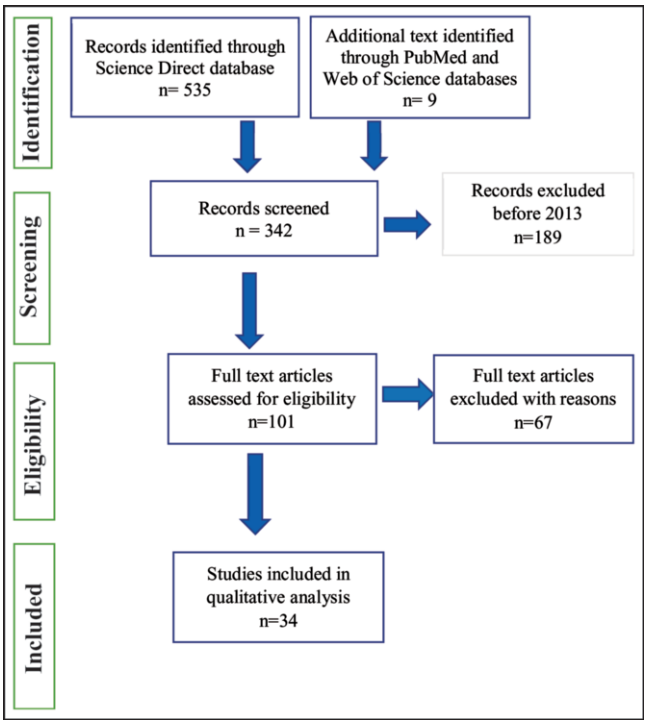

Figure-1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart.

titles and abstracts of articles and patents initially found were analysed. Literature was searched using key terms "Antimicrobial releasing periodontal scaffolds" primarily on Science Direct, PubMed and Web of Science search engines with a limitation to their registered published papers. Any article which was difficult to access was secondarily searched using Google Scholar search engine. Full copies of all potentially relevant articles were analysed by two reviewers. Any disagreement on eligibility of articles was resolved with mutual consensus (Figure-1).

Studies included were related to fabrication, characterisation and drug release from scaffolds used for periodontal regeneration, and those including different types of membranes and multiple drug delivery systems regarding periodontal regeneration.

Studies excluded were related to drug-releasing resins and antibacterial releasing cements as well as comparative studies, review articles and articles whose full text was not available.

Quality assessment

Quality of included studies was assessed by two individuals at different time intervals. The Cochrane statistical collaboration review guidelines were followed and results for Risk of Bias were calculated considering important aspects reported and elaborated as having low, medium and high risk for bias.[1]

Results

Of the 544 studies found, 34(6.25%) were selected (Figure-1). The studies were categorised into in-vitro (Table-1) group and another group comprising in-vivo and mixed studies (Table-2). Risk for bias was calculated for each study (Table-3).

The research trend pivoting towards use of antimicrobial-loaded scaffolds was seen to be growing since 2013 onwards (Figure-2). Employment of antimicrobials reported reduction in number of periodontal pathogens and promotion in terms of osteoblastic differentiation. Different drugs generally employed in periodontal ailments included tetracycline hydrochloride, beta tricalcium phosphate, metronidazole, doxycycline, ciprofloxacin, ampicillin, zinc phosphate, tri-calcium silicate and chitosan. Any of the selected antimicrobial agent was incorporated into the scaffold matrix by employing required fabrication methods, majorly obliging e-spinning and solvent-casting procedures. In cases where enhanced and modified properties were required, hybrid blends, composites and multiple layering

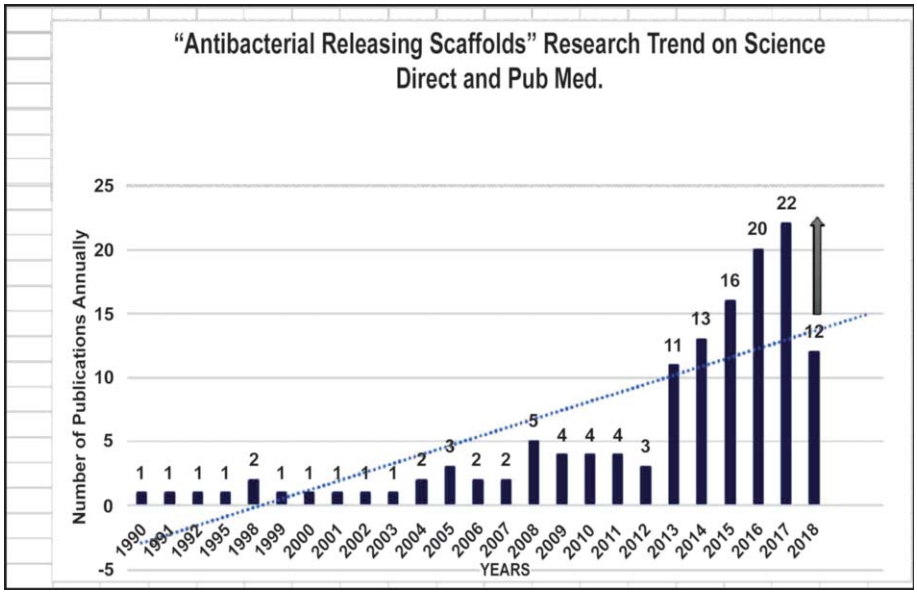

Figure-2: Research Trend of selected publications demonstrating an exponential increase year-wise, specifically from 2013 onwards (data extraction done till April 20, 2018).

Table-1: In-vitro studies for systematic review.

Citations	Study type	Therapeutic agent	Type of scaffolds used	Results
R.Ramirez-Augdelo et al[8]	Cytotoxicity & antibacterial (AB) activity evaluation	Doxycycline (DOX)	Electrospun (E-spun) fibers of poly-ε-caprolactone (PCL) + gelatin + Nano hydroxyapatite particles (nHA).	Synergistic effect of nHA & DOX exhibited bacterial growth inhibition.
Duruel, T., et al[9]	Evaluation of cellular function in cell cultures.	Alginate microparticles, IGF-1 carrier & PLGA, BMP-6 carrier	Chitosan(CS)/alginate/PLGA (hybrid scaffolds).	Proliferation & osteoblastic differentiation of cementoblasts with sustained drug delivery (DR) was observed.
Ana PF Monterio et al[10]	AB activity of 2 drug delivery systems for use as adjuncts in PD.	Tetracycline alone (TC) & TC/ β-cyclodextrin (TC:BCD)	Polycaprolactone (PCL) n-fibers.	Formation of TC: BCD inclusion complexes lead to better bioavailability & absorption of TC.
Meghan EE Wright et al[11]	Assessment of drug release	Ciprofloxacin bonded covalently to triethyliene glycol (TEG).	E-spun polycarbonate urethane (PCNU), biodegradable n-fibrous scaffold	Drug additives have potential to undergo fast dissolution & cell attachment due to phase separation from the fibers.
Ren Ke et al[12]	Fabrication & characterization.	Genipin crosslinker.	E-spun Polycaprolactone-gelatin hybrid membrane (PCL)	All n-fibers had uniform structure along with good MP & cytocompatibilty.
Saad B. Qasim et al[13]	Ease of integration of surface layer of GTR membrane with periodontium	Chitosan fibers of different orientation	E-spun CS membrane with low & high fiber orientation.	Random & aligned fibers were shown to be conductive to cellular attachments & viability increased with time.
P.R. Sivashinkari.et al[14]	Evaluation of DR, tissue repair & regeneration potential.	Growth factors: BFGF & dexamethasone.	CS based scaffolds containing growth factors.	Scaffolds were nontoxic & biodegradable, immobilized growth factors & showed sustained release.
Marina dos silva et al[16]	Analysis of biological properties.	Chlorhexidine	Pure CS & alginate (3 layered membrane)	Reduced cell viability.
W. Shao et al[17]	Evaluation of DR, AB activity & biocompatibility.	TCHC.	Bacterial cellulose membranes	Controlled DR, favorable biocompatibility & excellent AB activity.
G.Ivigilia et al[19]	Cell cultures evaluating MPs.	Reinforcement of biphasic Ca3(P04)2 particles in different size ranges.	Moldable CS-pectin hydrogel was used to mimic ECM of natural bone.	Ceramic particles enhanced MP of hydrogel + high osteoblastic proliferation was seen.
Dennis Schkarpetkin et al[21]	Cell cultures to access DR manner & AB effects	Ampicillin & metronidazole combination.	E-spun polylactide fibers.	The drug delivery system suppressed pathogenic bacteria & demonstrated controlled DR.
E A. Munchow et al[22]	Assessment of AB potential & MP of membranes (GTR/GBR).	Novel Zinc oxide (Zn0) n-particles loaded fibers	Poly-ε-caprolactone (PCL) and PCL/Gelatin PCL/Gelatin E-spun membrane.	Membranes showed good AB properties but slight reduction in MP but enhanced flexibility under wet conditions due to gelatin.
K. Jurczyk et al[23]	Bacterial adhesion study.	Silver particles.	n-structured Ti-45S5 bio glass plate	Significant decrease in S.mutans & S.aureus conc. on plate surface.
M. Ranjbar Mohammadii et al[24]	Drug carrying capacity of scaffolds.	TCHC.	PLGA, gum tragacanth (GT) & TCH were used to fabricate hydrophilic scaffold (blend & coaxial E-spinning).	Prolonged DR, good antimicrobial activity, cytocompatibility & MP favored their use.
K. Kanimozy et al[25]	To evaluate MP, porosity & AB	Methylcellulose (MC).	CS/poly vinyl alcohol (PVA) porous membrane.	Increase in MC, increased porosity & swelling.

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Citations	Study type	Therapeutic agent	Type of scaffolds used	Results
				Better elasticity in dry swollen state & good AB effect.
Min He et al[26]	Anti-microbial activity, DR, cytotoxicity testing.	Metronidazole.	Coaxial E-spun Core/sheath PCL/gelatin n-fiber membrane.	Core/sheath n-fibers showed good AB activity, favourable DR with minimal cytotoxicity & better cell adhesion.
Ariba Farooq et al[27]	Analysis of DR, cytocompatibility, pore size & thermal stability.	Piroxicam in different concentrations.	E-spun CS/PVA/HA n-fiber composite	Both fibers & film showed > thermal stability. > pore size, < fiber diameter. Initial burst DR & cytocompatibility was observed.
Saad B Qasim[29]	Cell culture study done for fabrication & characterization.	HA	Porous CS membranes fabricated via freeze gelation technique using solvents acetic acid & ascorbic acid	Membranes were resistant to handle in both wet & dry conditions. Good cellular activity. CS:HA composite has the potential to be used as a core layer in GTR membranes.
R.Ruggiero et al[30]	Evaluation of DR & degradation rate of membrane.	TC	Commercial cellulose acetate with DS= 2.45, which was partially deacetylated & impregnated with TC.	Rapid DR for 8 hrs followed by slow DR + degradation in 99 days. Can potentially serve as an adjunct in GTR.
P. Gentileet al[31]	DR evaluation	Metronidazole	PLGA aminolysed & modified layer by layered technique (LBL).	LBL created multi-layered coating on PLGA for antibiotic incorporation. Controlled drug delivery upto 80% with small loaded drug concentration.
Yu Xiao et al[32]	DR, MP, AB test against P.gingivalis & cytotoxicity.	Metronidazole	A glucose sensitive CS-polyethylene oxide hydrogel.	Controlled DR of metronidazole in the presence of glucose stimulus with > release in > glucose conc. & minimal cytotoxicity.
Bryan R. Orellana et al[33]	Evaluation of MP & DR potential.	Metronidazole loaded PLGA particles.	Double layered CaSO4 based composite membranes having a shell & core geometry.	The shell & core form decreased MP of membrane but controlled DR was obtained.
K Jumana-Thevi et al[34]	Cell culture studies characterizing triple layered membrane.	Lauric acid (LA) to promote bone growth + Nano apatite (Nap) as antibacterial.	Triple layered PLGA, using single step combining techniques of solvent casting & thermally induced solvent leaching.	NAp & LA combination showed > tensile strength & elastic properties than pure PLGA + good cell viability & bacterial inhibition.
N. Sindhura Reddy et al[35]	DR potential	Tetracycline n-particles.	Injectable CaSO4 based composite membrane.	Composite beads demonstrated good cytocompatibility, sustained AB release.
A.P Hurt et al[36]	Evaluation of biocompatibility & bioactivity	Tobermorite as a bioactive material.	CS & calcium silicate hydrate phase (composite) GTR membrane.	Formation of HA crystals on surface of tobermorite particles indicated invitro bioactivity & enhanced cell viability.
Backlund et al[39]	DR study	Nitric oxide	Dendrimer & silica based nitric oxide releasing scaffolds	Marked reduction in periodontal pathogens but minimal effects on caries associated bacteria.
N. Hild et al[40]	Demonstrating pH dependent AB activity of scaffold	Bioactive glass (BG) and PLGA	Pure PLGA & composite of nano-sized BG/PLGA.	Pure PLGA showed better AB activity than n-composite due to its ability to sustain pH longer.

Table-2: In-Vivo and Mixed Studies for systematic review.

Citations	Study type	Therapeutic agent	Type of scaffolds used	Results
MG Gandolfi et al[7]	Calcium ions release was assessed with pore size.	Ca_2SiO_4 & $CaHPO_4$.	PLA-based porous scaffolds doped with Ca_2SiO_4 & $CaHPO_4$.	Mineral-doped scaffolds released Ca+2 ions. Surface pores ranged 10-20µm in pure PLA to 10-100µm in PLA-10CaSi with minimal cytotoxicity.
K.Maryz et al[15]	Evaluation of osteoconductive effect.	TC	$CaSO_4$ based n-composite (HAP/β-TCP) undoped & co-doped with Er^{3+}/Yr^{3+} loaded with different dosages of TC.	Highest dose of TC released seen after 24hrs. Combinations had regenerative, fluorescent & AB properties on h- ADMCs.
W J. Bae et al[18]	Determination of Human periodontal ligament stem cells (h-PLSCs) & osteoblasts cell cultures for 14 Days	Sodium triphosphate (STP), sodium hexa-metaphosphate (SHMP)	Various concentrations of STP & SHMP were used.	Both STP & SHMP promoted osteoblastic proliferation + differentiation in in-vitro cases while STP showed bone regeneration in-vivo.
Bor Shiun lee et al[20]	Fabrication and characterization of multilayer membrane for periodontal bone regeneration in dogs.	Epigallocatechin-3-gallate EGCG for bactericidal activity & lovastatin for controlled release.	A tri-layer functional chitosan (CS) membrane.	Good bactericidal activity & higher percentage of bone regeneration due to regulated DR.
Jiajia Xui et al[28]	Evaluation of AB loaded n-fiber membrane with adjustable degradation.	Metronidazole	E-spun poly (ε-caprolactone)-gelatin n-fiber membrane.	Good strength & controlled DR with higher rate of biodegradation in increased gelatin conc., controlled by altering PCL: Gelatin ratio.
Rui Shi et al[37]	Biocompatibility, AB property, physical properties & degradability in male rabbits.	Metronidazole, gelatin & hydrogen acetic acid (HAC) used in different integrations	E-spun PCL n-fiber membrane.	1< HAC imparts good tensile & physical properties. 2<Favourable antimicrobial activity. 3< Gelatin improved degradation & cytocompatibility.
Jiajia Xue et al[38]	Evaluate antimicrobial property, chemical, physical and MP were tested in rabbits.	Metronidazole (MNA).	E-spun polycaprolactone (PCL) nanofibers at different concentrations.	Sustained DR with good anti-microbial activity. Excellent barrier function with good cell proliferation, but lesser inflammatory response in n-fibers.

of potential matrix bases were utilised for restrained drug release.

Discussion

Scaffolds: Fabrication of different type of scaffolds employs various methods. New materials are continuously being synthesised to achieve the required properties of injectability, biodegradability, low cytotoxicity, nano-scale fibres and controlled drug release. It is now a common practice to load porous matrix bases with different antimicrobial agents which render impressive results.[3,7]

Poly-ε-caprolactone (PCL) is a hydrophobic polymer approved by the Food and Drug Administration (FDA) with good resorption rate. PCL / Gelatin (GEL) scaffold nano-fibrous composite is used successfully for bone regeneration and wound healing and its loading with anti-inflammatory and other materials. PCL / GEL hybrid fibres, when loaded with zinc oxide (ZnO) nanoparticles demonstrated different mechanical strengths in wet and dry conditions plus optimal antimicrobial activity.[8]

Chitosan, a natural polymer, is being used as a scaffolding material due to its good biocompatibility, antibacterial, antifungal and mechanical properties and resorption rate. Chitosan-pectin hydrogel extracellular matrix (ECM) is used for alveolar bone regeneration.[9] They also inhibit P. gingivalis in periodontitis by sustained drug release.[10] Hybrid of chitosan with other materials makes it one of the most commonly used scaffold material showing excellent results.[11] Cell culture studies of chitosan / Alginate / polylactic-co-glycolic acid (PLGA) hybrid scaffolds are reported to promote cell adhesion, proliferation and differentiation with minimal cytotoxicity.[9]

Biodegradable polymers, like polylactic acid (PLA) and

Table-3: Risk of bias.

Study	Blinding of operator	Drug release measured	Multiple controls	Antimicrobial efficiency calibrated	Selective Reporting	Risk of BIAS
(2) (7)	N	Y	Y	N	N	Medium
(3) (8)	N	N	Y	Y	N	Medium
(4)	N	Y	Y	N	Y	Low
(5) (10)	N	Y	Y	Y	N	Low
(6, 7) (11)	N	Y	N	N	N	High
(7) (12)	N	N	Y	N	Y	Medium
(8) (13)	N	N	Y	Y	N	Medium
(9) (14)	N	Y	Y	N	Y	Low
(10) (15)	N	Y	Y	Y	N	Low
(11) (16)	N	Y	N	Y	N	Medium
(12) (17)	N	Y	N	Y	Y	Low
(13) (23)	N	N	Y	Y	N	Medium
(14) (18)	N	Y	Y	N	N	Medium
(15) (19)	N	N	Y	N	N	High
(16) (20)	N	Y	N	Y	N	Medium
(17) (21)	N	Y	Y	Y	N	Low
(18) (24)	N	Y	Y	Y	N	Low
(19) (32)	N	Y	N	Y	N	Medium
(20) (25)	N	Y	Y	Y	N	Low
(21) (22)	N	N	Y	Y	N	Medium
(22) (26)	N	Y	Y	Y	N	Low
(23) (27)	N	Y	Y	N	N	Medium
(24) (28)	N	Y	N	Y	N	Medium
(25) (29)	N	N	Y	N	N	High
(26) (30)	N	Y	Y	Y	N	Low
(27) (31)	N	Y	Y	Y	N	Low
(28) (33)	N	Y	N	Y	Y	Low
(29) (34)	N	Y	Y	N	N	Medium
(30) (35)	N	Y	N	Y	Y	Low
(31) (36)	N	N	Y	N	N	High
(32) (37)	N	N	Y	Y	N	Medium
(33) (38)	N	N	Y	Y	N	Medium
(34) (39)\	N	Y	Y	Y	N	Low
(35) (40)	N	N	Y	Y	N	Medium

polyglycolic acid (PLG) hold special importance due to their bioactivity and biodegradability and are used alone or in combination.[10,11] They are widely used in the form of PLGA and poly-L-lactide (PLLA). Use of electro-spun PLA scaffolds loaded with antibacterial drugs, like metronidazole and ampicillin, leads to inhibition of pathogenic bacteria in both endodontic and periodontal infections.[11] PLGA scaffolds doped with drugs had favourable biocompatibility, biodegradability, cell viability, mechanical properties along with sustained drug release.[12]

Other scaffold biomaterials include bacterial cellulose membranes, calcium sulphate-based nano-composites, electro-spun polycarbonate urethane (PCNU), nanostructured bioglass Titanium (TI)-45S5, nano-hydroxyapatite crystals (nHA), ZnO nano-particles, different growth factors and commercial calcium acetate membranes. All of these have reported to serve as acceptable drug delivery vehicles in addition to having adequate mechanical properties, favourable degradation rates, good biocompatibility and controlled release of drugs.[13,14]

Effect of Antimicrobial Agent Incorporation: Scaffolds of varying composition differed in their inherent properties in the drug delivery system. One of the most routinely used antimicrobials is tetracycline (TCH), a broad-spectrum antibiotic. The inclusion of tetracycline hydrochloride (THC) into chitosan / polyvinyl alcohol (PVA) nano-fibres showed good antibacterial properties due to initial burst drug release, resulting in effective inhibition of targeted bacteria involved in periodontitis. Out of 34 studies included, 8 used THC as an antibacterial drug, depicting TCH as a promising antibiotic for periodontal use. However, due to the emergence of

resistant strains against TCH, other options are more validated.[15]

Various promising antimicrobials, including metronidazole (MNZ) and doxycycline (DOX), upon investigation demonstrated decrease in pathogenic activity at the targeted site with minimal cytotoxicity, making them favourable for use in procedures like GTR / GBR.[16] DOX showed anti-inflammatory, anti-proliferative, anti-angiogenic and osteoclast inhibitory properties as well. DOX inclusion into electro-spun nano-fibres imparted comparative antimicrobial activities with no cytotoxicity.[17-19] MNZ fusion with other materials, like acetic acid, gelatin or hydroxyapatite (HA) crystals enhanced mechanical properties and increased durability of scaffolds.[20] DOX, a broad-spectrum bacteriostatic, acts by inhibiting protein synthesis.[21]

In modern dentistry, employment of nano-particles (NPs) in different dental materials has gained popularity. Inclusion of ZnO NPs into PLGA / chitosan composite imparts antimicrobial activity and better mechanical properties.[22] Chitosan fibres with nano HA (n-HA) depicted better alveolar regeneration and healing.[13] Apart from antimicrobial agents, various therapeutic agents used included ciprofloxacin for rapid dissolution and drug release, tobermorite as an active glass material for periodontal regeneration, and nano-apatite crystals having adequate antibacterial activities.[23-25]

Antimicrobial agents in periodontal scaffolds inhibit microbial colonies and improve bone regeneration and growth. In the light of the data, it can be seen that with decrease in microbial count, increased cell adhesion, proliferation and differentiation was observed due to the inclusion of favourable agents.[20] All of the therapeutic agents included into the scaffolds demonstrated compatibility with other biomaterials used, such as titanium, calcium silicate and bio-glass. Majority of these agents did not affect mechanical properties of scaffolds, but a few of them, such as tetracycline hydrochloride, chitosan and beta-tricalcium phosphate, enhanced their properties while others exhibited different results in dry and wet states.[22] Although biomaterials, like autologous stem cells, bio-glass, polytetrafluoroethylene (PTFE)-based scaffolds, have been tested clinically in periodontal regenerative therapy, majority of antimicrobial-loaded scaffolds need to go through clinical trials which would confirm their action.

Conclusion

New antimicrobial-containing scaffolds are emerging rapidly with better properties and enhanced antibacterial activity. This emerging trend is not only improving the inhibitory effect of bacterial growth, but is also making a favourable environment for cell proliferation and differentiation, resulting in alveolar bone repair and re-growth. Available data demonstrated potential upsurge in the use of antimicrobial-loaded scaffolds in evidence-based dentistry for periodontal regeneration. However, more clinical trials are needed in order to make them a clinically acceptable choice and to confirm their effectiveness against dental pathogens and alveolar bone regeneration.

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