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Probiotics -The Future of Bacteriotherapy in Endodontics: A Review

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Abstract:
Endodontics is a specialty in dentistry concerned with the prevention, diagnosis, and treatment of diseases or injuries to the dental pulp and periapical tissues. The basic need of an endodontic treatment is to maintain the health of the tooth and its function in the oral cavity for a longer period of time in human life. Success in endodontic treatment relies on the triad of debridement, thorough disinfection of the root canals, and obturation, with all aspects being equally important. Mechanical instrumentation cannot sufficiently disinfect the root canals, and so disinfectants in the form of irrigation solutions are imperative to eradicate the microflora. Over a period of time, a wide array of chemical irrigants have been popularized with the motive of killing the microflora, dissolving necrotic tissue, removing the smear layer, and lubricating the canal without irritating the healthy tissues. Recently, the role of Probiotics in dentistry have been emphasized due to its antimicrobial action against various pathogenic oral microflora. In this direction, the paper highlights the review of various scientific literatures and research work on the possible uses of Probiotics in the field of endodontics to manage endodontic infections and to promote healthy ecology and healing.

Key Word: Probiotics; Lactobacillus; Bifidobacterium; Poloxamer; E. fecalis; C. albicans; Endodontic infections;

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I. Introduction

Periapical pathology involves inflammation and destruction of periradicular tissues which is generally a sequel to pulpal inflammation or necrosis with necrotic byproducts and inflammatory mediators spreading through apical foramen to initiate a periapical lesion. Failure to effectively eliminate the microorganisms and noxious substances possibly lead to persistent inflammation and impaired healing. More than 90% of the microflora present in root canals with necrotic pulp and diseased periapices, are obligate anaerobes usually belonging to the genera Fusobacterium, Eubacterium , Prevotella, Porphyromonas, and Peptostreptococcus.[1,2]

Success rates of endodontic treatments which ranges from 86% - 98% is gauged by the resolution of clinical signs and symptoms, as well as the radiological findings of the treated tooth. An Endodontic treatment can be called a failure if it causes recurrence of clinical symptoms along with the presence of a periapical radiolucency.[3]

Causes of endodontic failure :

A multitude of factors have been associated with the failure of endodontic treatment. They are persistence of bacteria (intra-canal and extra-canal) which could be due to inadequate debridement or disinfection, inadequate filling of the canal or overextensions of root filling materials, improper coronal or apical seal, missed or untreated canals, iatrogenic procedural errors such as poor access cavity design, ledges, perforations, or separated instruments. One of the foremost causes of endodontic failure is either persistent or secondary intra-radicular microbiological infection.[4]

Several microorganisms have the ability to co-aggregate and adhere to the radicular dentin, forming dense biofilms that lead to persistent infection. These biofilms harbor the microbial colonies, with fluid channels that transport nutrient substrates, waste metabolites and signal molecules, and hence eradication of endodontic biofilms play a vital role in the successful outcome of the root canal therapy. Improper disinfection protocols, poor coronary seal and so on, lead to secondary infections which can set in any time after the initiation of endodontic treatment. Persistent infections are remnants of primary or secondary infections and are usually caused by the microflora that are resistant to all the intracanal antimicrobial debridement procedures and can survive in all harsh environments.[5,6]

Previous studies conducted by Pinheiro et al have revealed the fact that, Enterococcus fecalis (E. faecalis) is the most prevalent microorganism found (45.8%) in root canals of previously endodontically treated tooth, followed by Parvimonas micra(24%), Fusobacterium, (6.7%) and Propionibacterium (3.3%) and that the presence of E. faecalis is more frequent in secondary infections (89.6%) than in primary infections.

Candida albicans is the most frequently isolated fungi from teeth with post-treatment, persistent apical periodontis.(Fig.1 and 2). The biphasic nature of C. albicans allows it to readily co-aggregate and form complex biofilms that propagates the infection further.[7]

Enterococcus faecalis :

Enterococcus faecalis (E. fecalis), a gram-positive opportunistic coccus is a facultative anaerobe, that can adapt to any harsh environment with complex ecology.

Characteristics of E. fecalis that make it resistant to the conventional disinfection protocols, are:

Ability of E. fecalis to survive in environment with low oxygen levels, poor nutrition, low or highly alkaline pH of upto 11-12, adverse temperatures ranging between 10°- 60°, hyper or hypotonicity. E. fecalis can resist intracanal medicaments like $Ca(OH)_2$ due to its proton pump, can acquire antibiotic resistance and resists the host defence by virulence traits like lipoteichoic acid, endotoxins, bacterial surface adhesins, lytic enzymes and stimulates leukocytes to release inflammatory mediators.

E. faecalis forms well-organized, complex biofilm,(Fig.3), in which the bacterial cells become tolerant to antibiotics of higher concentrations than are required to eliminate planktonic cells. These biofilms harbors the microorganisms in inaccessible regions like apical deltas, accessory canals, and isthmi.[8,9]

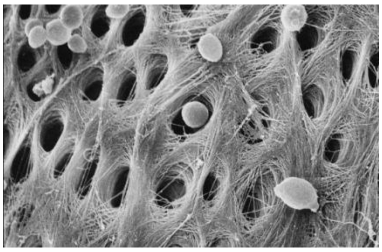

Fig.1. Scanning electron micrograph of C. albicans blastospores on root canal wall

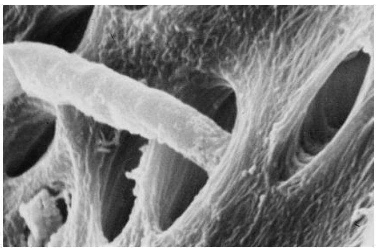

Fig. 2. Scanning electron micrograph of C. albicans hyphae penetrating dentinal tubule

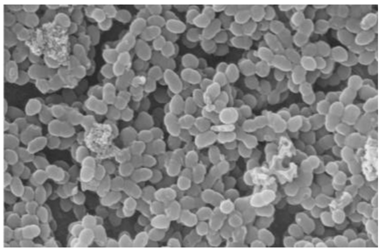

Fig. 3. Stereomicroscopic Image of E. fecalis biofilm on a root canal wall

The treatment options sought against E. faecalis till date are :

A) ***Irrigants and intracanal medicaments*** : these improve the outcome of endodontic therapy by reducing the microbial load from the root canal system. The most commonly used irrigants are saline, sodium hypochlorite, chlorhexidine, and EDTA. Saline is used as irrigant due to it flushing action on superficial debris, but has poor dissolving and antimicrobial activity. Whereas sodium hypochlorite is a potent tissue dissolvent and antimicrobial agent, but is highly toxic if exposed to periapical tissues. Chlorhexidine(CHX) has a broad spectrum antimicrobial action with added advantage of substantivity, but is a poor tissue dissolvent. EDTA chelates the minerals and removes the smear layer, when in direct contact with the root canal wall, but has no antibacterial activity and can erode the dentin if left in canal for a longer time.[10]
Other less commonly used irrigants are cetrimide, MTAD, Tetraclean, Qmix and so on. Jeison et al. demonstrated in an in-vitro study that both 1% cetrimide and Triple antibiotic paste reduced the viability of E.fecalis significantly better when compared to CHX and calcium hydroxide.[11] The efficacy of BioPure MTAD (mixture of doxycycline, citric acid and a detergent) against E. fecalis and C. albicans was demonstrated by Davis et al., suggesting that BioPure MTAD showed significantly more zones of microbial inhibition than 5.25% NaOCl and 2% CHX.[12]

B) ***Activation methods during irrigation:*** various methods that enhance the efficacy of irrigants are sonic and ultrasonic activation, laser activation, photon-induced photoacoustic streaming (PIPS) technique and so on. The mechanical energy produced by ultrasonic activation causes cavitation, heating and acoustic streaming of the irrigant that dislodges the debris from the canal wall.

The photothermal effect of Lasers, alter the osmotic gradient of the bacterial cell, causing cellular swelling and death. PIPS creates successive strong photoacoustic shockwaves that streams irrigants three dimensionally without rising of temperature.[13]

A study conducted by Mohammed et al. showed that laser-activated irrigation using an Er:YAG laser and photon-induced photoacoustic streaming (PIPS) technique in conjunction with NaOCl was the most effective method for removing E. faecalis biofilm from the root canal system when compared with the other activation techniques like sonics and ultrasonic irrigation techniques.[14]

The major drawbacks of synthetic antibacterial agents are hypersensitivity, immune suppression, cytotoxicity, mutagenecity, discoloration of the tooth structure, and most importantly acquired resistance to the drugs.

To overcome these drawbacks, the use of antimicrobial agents from herbal plants (phytomedicine) have been widely employed. In dentistry phytomedicine has been used as anti-inflammatory, antbiotic, analgesic, sedative, also as intracanal medicaments and irrigants in endodontics.[15]

C) ***Natural agents/ herbal extracts :*** various herbal extracts such as aloe vera, neem, propolis, triphala, turmeric, passion fruit juice, tea tree oil, Morinda Citrifolia (noni), and so on, have been studied for their antimicrobial efficacy and application in endodontics.

A study conducted by Jayahari et al., suggested that the alcoholic and aqueous extracts of passion fruit juice showed antibacterial effect against E. fecalis.[16] Santosh et al., in a study reported that the neem leaf extract had significantly better antimicrobial action against E.fecalis and C.albicans when compared to 17% EDTA, with added advantage of being biocompatible and natural antioxidant.[17] Larissa et al., confirmed in an study that grape seed extract had antimicrobial efficacy against E. fecalis and hence had the possibility to be employed in clinical scenarios as irrigant solution in endodontic therapy.[18]

The major advantages of using herbal alternatives are ease of availability, increased shelf life, cost-effectiveness, lack of microbial resistance reported so far, and low toxicity.[15]

II. Newer Therapy - Probiotics In Oral Health

Probiotics refer to live bacteria that confer a health benefit to the host. In 1965, Lilley and Stillwell coined the term “Probiotic”. In 2002 WHO defined probiotcs as, live microorganisms which when administered in adequate amounts, confer health benefits on the host beyond basic nutrition. These have been used successfully in medicine, especially to treat the gastrointestinal disorders. The most widely used species for bacteriotherapy are the strains of Lactobacillus and Bifidobacterium as probiotics.

Probiotic bacteria was introduced into dentistry as oral “replacement therapy” for prevention and treatment of oral diseases, where they appear to act through colonization resistance and immune modulation. It has been shown that probiotics are effective in controlling gingival inflammation, reducing plaque levels, prevention of various periodontal diseases, treating halitosis, candidal infections, and also in prevention of dental caries. Periodontal pathologies are caused by numerous pathogens that are common with those causing endodontic infections, and hence utilizing probiotics within the root canals may also prove to be advantageous in combating endodontic infections.[19,20]

i. ***Species used as probiotics :*** Composition of probiotics include species of bacteria, yeast, or mold species are used as probiotics. But most often bacterial species are used, they include (Fig.4) :

a. Lactic acid producing bacteria: Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus rhamnosus, Lactobacillus reuteri, Lactobacillus lactis.
b. Non-lactic acid producing bacteria : Enterococcus faecium, Esherichia coli, Streptococcus thermophiles, Propionibacterium
c. Bifidobacterium species : Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium adolescentis, Bifidobacterium longum, Bifidobacterium breve etc
d. Non-pathogenic yeast : Sacchromyces boulardii
e. Non-spore forming: Coccobacillus

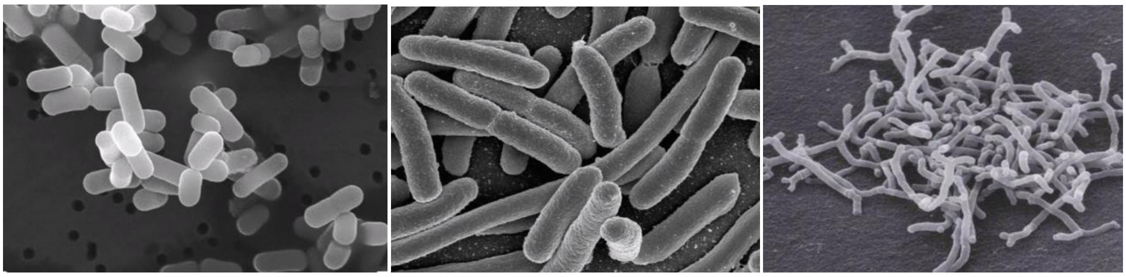

Fig. 4. Scanning electron micrograph of Lactobacilus reuteri, Lactobacillus acidophilus and Bifidobacterium longum in sequence

ii. ***Mechanism of action of probiotics :*** They resists the colonization of other bacteria, by competing for growth factors, nutrients. Probiotic species co-aggregate with the oral commensals and changing the composition of the biofilms and produce various antimicrobial metabolites and enzymes that act against pathogens. They induce immunomodulation by decresing the production of pro-inflammatory cytokines like IL1ß, TNF-α, IL-8, and increasing the production of IgA, and other anti-inflammatory mediators.[21]

iii. ***Probiotics are supplied in any of the following basic ways :*** As culture concentrates added to beverages (fruit juices) or food (soya bean), or can be inoculated into prebiotic fibers, milk or milk-based food (dairy products, yoghurt, sour cream, cheese), as concentrated and dried cells packaged into dietary supplements in form powder capsules, gelatin tablets etc.[22] Recently probiotics have been combined with Poloxamer 407, a non-ionic copolymer of polyethylene and polypropylene oxide. Poloxamer has been used as jelling agent for various surface applied formulations including fluoridated dentifrices.

III. Concept Of Probiotics In Endodontics

The traditional concept of endodontics narrows down to the fact that all the microorganisms should be eradicated from the root canal system irrespective of their pathogenecity. Due to the complexities of root canal morphology such as the presence of multiple accessory and lateral canals, it is difficult to obtain complete sterility within any root canal system. But studies have suggested that atleast a significant reduction in the bioload of microorganisms can be acheived. The current and emerging trends in microbiology states that a better modality to treat a microbial infection is to achieve and maintain a state of equilibrium within the human microbiome and to shift towards a more favorable ecology conducive of healing.[23]

Novel concept of Bacteriotherapy in Endodontics is to replace the pathogenic bacteria by healthy bacteria, and normal flora. Though the role of probiotics in endodontic therapy has not been extensively evaluated, there are several in-vitro studies that highlight their potential antimicrobial activity against endodontic pathogens.

As described earlier E. faecalis and C. albicans are the most frequently isolated microorganisms from root filled teeth with apical periodontitis, thereby the complete elimination of E. faecalis and C. albicans is quite challenging and hence these particular microorganisms were selected for most of the studies.

In-vitro studies could demonstrate the antimicrobial activity of commercial probiotics composed of various species of Lactobacillus, Bifidobacterium and Streptococci against E. faecalis and C. albicans. Studies also revealed that even the cell free supernatant with metabolic by-products of the probiotic samples could potentially diminish the growth of endodontic pathogens and hence can possibly substitute the probiotic microorganisms themselves.[24]

Recent scientific literatures have utilized the Lactobacillus species as experimental probiotic and the following inferences were drawn :

Lactobacillus reuteri produces metabolites that are broad-spectrum antimicrobial factors like reuterin and reutericyclin, that inhibit microbial DNA synthesis, thereby preventing the growth of biofilms comprising of Gram-positive and negative bacteria, fungi, protozoa.[25]

According to Kim et al., a study conducted demonstrated that the Lipoteichoic acid produced by Lactobacillus planatarum inhibited the preformed multispecies biofilm formation by controlling quorum sensing, gene expression and inhibiting exopolysaccharides production. Lipoteichoic acid inhibits not only mono-species, but also multi-species biofilm consisting of Actinomyces naeslundii, E. faecalis, Lactobacillus salivarius, and Streptococcus mutans. These anti-biofilm effects are enhanced when lipoteichoic acid is combined with conventional intracanal medicaments like calcium hydroxide or chlorhexidine.[26,27]

Lactobacillus rhamnosus and Lactobacillus acidophilus when systemically administered in mice, lowered the inflammatory infiltrate and the expression of pro-inflammatory cytokine (IL-1b and IL6) with concurrent rise in the expression of anti-inflammatory cytokine(IL-10) thereby reducing the overall severity of apical periodontitis.[28]

A recent study conducted by Rai et al., aimed to compare the antimicrobial efficacy of probiotic strains-Lactobacillus acidophilus, Lactobacillus casei and Lactobacillus rhamnosus, against the gold standard irrigant, 5.25% sodium hypochlorite and saline at 48hours and one week. The findings suggested that 5.25 % NaOCl produced significantly larger zones of inhibition followed by the probiotic strains at both the time periods, with saline being totally ineffective against E. fecalis and C. albicans. This study could infer that all the probiotic strains used were able to prevent the growth of E. faecalis and C Albicans and can probably be an effective antimicrobial substitute to saline as an irrigant.[29]

Consumption of probiotic yogurt significantly attenuated the growth of Streptococcus mutans in the saliva and hence, could lower the incidence and severity of enamel demineralization in patients undertaking fixed orthodontic therapy.[25]

A study conducted by Bohora et al., reported the antimicrobial efficacy of commercially available probiotics containing Lactobacillus species against E. fecalis and C. albicans in biofilm and planktonic stages. The study also suggested the use of a novel delivery vehicle into the root canal by utilizing 30% Poloxamer 407 mixed with Man, Rogosa and Sharpe (MRS) or Tryptic soy broth (TSB) containing probiotics. Poloxamer shows inverse thermosensitivity, forming aqueous solutions at low temperatures (4°C), but gels at higher temperatures, hence can be used as ideal delivery vehicle for intracanal medicament.[30,31]

In a similar study conducted, antimicrobial activity of Lactobacillus plantarum, Lactobacillus rhamnosus and Bifidobacterium bifidum against E. fecalis and C. albicans in both planktonic stage and biofilm stage was assessed by measuring the zone of inhibition and colony forming units produced by the pathogenic strains. The results showed that both the probiotic groups (lactobacilli and Bifidobacterium) exhibited antimicrobial activity against E. faecalis and C. albicans in their planktonic stages, and in biofilm stage, all three probiotics showed growth reduction for E. faecalis, while lactobacilli group showed reduction in C. albicans colonies. Application phase of this study, evaluated the potential efficacy of 30% poloxamer 407 as delivery vehicle for probiotics into the root canal system and concluded that poloxamer-based probiotic mixture can be left within the root canal systems for approximately one week as intra-canal medicament, and that the remnants of healthy probiotic microbes would render an environment in the root canal sysytem that is more favourable for healing.[32]

A recent study aimed to test probiotic of Lactobacillus rhamnosus (L. rhamnosus) as an experimental irrigant in the presence of the established post-endodontic treatment disease by E. faecalis. L. rhamnosus was cultured in De Man, Rogosa, Sharpe (MRS) broth medium at 37°C for 48 hrs. The experimental probiotic irrigant was formulated through inoculation of L. rhamnosus in sterile distal water. The results showed that E. faecalis colonies significantly decreased from preirrigation to after 24 hrs post irrigation with probiotic irrigant. The results concerning the survival profile for both bacterial growth E. faecalis and L. rhamnosus revealed that the mean colony count for L. rhamnosus after immediate irrigation and post-irrigation was statistically significantly higher than for E.faecalis and hence L. rhamnosus could be used as a natural, safe probiotic irrigant along with a suitable vehicle.[33]

IV. Conclusion

The novel approach of bacteriotherapy with probiotics seem to be challenging, yet a promising adjunct for antimicrobial treatment of the root canal systems, with the added advantages of being natural and minimally toxic. Probiotic micro flora not only eradicates the endodontic pathogens, but also might prevent their re-colonization in the root canal systems, thereby reducing the probability of endodontic failures and improving the long-term success of root canal treatment. Poloxamer, as a vehicle for intra-canal medicament or root canal irrigant holds a new avenue to deliver probiotics into the root canal system. Literature on probiotics cannot be generalized since they vary according to the strain, dosage, frequency, experimental models and methods.

Therefore further in-vitro and in-vivo studies are essential in order to evaluate the efficacy of Probiotic usage in endodontics and derive evidence based treatment outcomes.

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