The Antimicrobial Effects of Poly(Lactic-Co-Glycolic Acid)/ Xylitol Nanoparticles on Microorganisms Causing Dental Caries (In Vitro Study)

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Abstract

Background: Many people all around the world suffer from tooth decay, a chronic infectious disease that can lead to tooth loss. *Streptococcus mutans* and *Candida albicans* are typical microorganisms involved in the caries process. Nanotechnology is one of the most exciting new developments in dentistry and can be used in the prevention of tooth. Xylitol's antimicrobial action can be enhanced by loading it onto poly(lactic-co-glycolic acid, or PLGA) nanoparticles. **Objective:** The purpose of study this is to evaluate the effectiveness of PLGA/xylitol nanoparticles as an antimicrobial agent on microorganisms causing dental caries. **Materials and Methods:** Samples from pure isolates of the bacteria and candida were kept in nutrient agar in a fridge until needed for the investigation. The antimicrobial activity of PLGA/xylitol nanoparticles produced using solvent evaporation was evaluated. Using the agar well diffusion method, we evaluated the sensitivity of *S. mutans* and *C. albicans* to various concentrations of nanoparticles with that of a positive control [chlorhexidine (CHX) 0.2%] and a negative control (de-ionized water). The zone of inhibition is measured across the diameter of each well. A serial dilution method was used to establish the minimum inhibitory concentration of nanoparticles against *S. mutans* and *C. albicans* and then determined minimum bactericidal concentration and minimum fungicidal concentration. **Results:** The results demonstrated the effectiveness of PLGA/xylitol nanoparticles in preventing bacterial and fungal development. As the concentration of nanoparticles increased, the diameter of zones of inhibition against *S. mutans* and *C. albicans* grew. Mean values of inhibition zones for *S. mutans* at 7.5%, 10%, 15%, and 20% were greater than CHX 0.2%. Nonetheless, for Candida, the mean values of inhibitory zones are still lower than CHX 0.2% at all concentrations with a statistically significant difference ($P < 0.05$). **Conclusion:** PLGA/xylitol nanoparticles are effective in preventing the growth of the microorganisms responsible for tooth caries. Although it is effective against *S. mutans*, its impact on *C. albicans* is much lower. The synergistic action of xylitol and PLGA nanoparticles could be responsible for this antimicrobial activity. This treatment could be considered as a way of preventing dental caries.

Keywords: *Candida Albicans*, nanoparticles, PLGA, *Streptococcus mutans*, xylitol

Introduction

Dental caries, a prevalent chronic infectious illness predominantly caused by cariogenic bacteria *Streptococcus mutans*, that adhere to teeth. Mutans streptococci is a gram-positive, facultatively anaerobic, catalase-negative bacteria that is frequently found in human mouths. The *mutans streptococci* are from the family: Lactobacillaceae, genus*: Streptococci* and tribe: *Streptococci*.[1] In the early stages of dental caries, *Streptococci mutans* (*S. mutans*) and *Streptococci sobrinus* (*S. sobrinus*) are the most closely related species. Two species of streptococci belonging to the "Mutans group."[2,3] *Streptococcus mutans* attaches to other plaque bacteria and to the enamel salivary pellicle. They increase the risk of dental cavities because they are acidogenic and acidouric.[4] Many investigations have

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determined the function of *S. mutans* in the onset of dental caries in both experimental animals and people.[5-7] The dimorphic yeast *Candida albicans* (*C. albicans*) is highly gram positive.[8] On specific media, it creates smooth, pasty convex colonies that range in color from creamy to white.[9] The human gastrointestinal and genitourinary systems contain commensal *C. albicans*, which can also thrive outside the human body.[10,11] Infections caused by *C. albicans*, an opportunistic pathogen, include thrushes in infants and chronic atrophic candidiasis (denture-induced stomatitis) in adults.[12-14] *S. mutans* and *C. albicans* interact to cause severe oropharyngeal illnesses and increase risk of dental caries.[15,16] According to some studies, there is a connection between *C. albicans* and dental caries in children and young adults.[17-19] Because of their small size and ability to enter cells, nanoparticles are advantageous; in that they release drugs more effectively, have lower MICs (minimum inhibitory concentrations) and MBCs (minimum bactericidal concentrations), and thus can increase antimicrobial activity with using less of the drug.[20] Many research demonstrated the antimicrobial impact of certain nanoparticles.[21-23] A copolymer of poly lactic acid (PLA) and poly glycolic acid is known as poly(lactic-co-glycolic acid, or PLGA). It is the biomaterial that has received the most attention in terms of both its structure and its function, and it is now being employed for medication delivery.[24] PLGA nanoparticles may be successful in many fields of dentistry such as endodontology, cariology, dental surgery, periodontology, and implantology.[25] It has been demonstrated that the tooth-friendly sugar alcohol xylitol has both cariostatic and noncariogenic effects. It decreases the prevalence of dental caries by inhibiting the growth of *S. mutans* and *C. albicans* and prevents plaque from producing acids and polysaccharides. It can be taken in the form of gum or mints which enhances mineral and alkaline flow from small salivary glands, increasing the saliva's buffering ability against acids and assisting in the repair of tooth damage.[26,27] The incorporation of xylitol into nanoparticles, such as PLGA nanoparticles, can enhance its antimicrobial action.[28] This study will evaluate the impact of PLGA/xylitol nanoparticles on salivary *S. mutans* and *C. albican* (in vitro study), as there has not been any research done on the subject [Figure 1].

Materials and Methods

Sample collection

Twenty pure isolates (10 for bacteria and 10 for candida) were collected from Baghdad hospital laboratories and diagnosed according to morphological characteristics, biochemical test, and VITEK 2 device. They were kept in nutrient agar in a fridge until needed for the investigation

Preparation of poly(lactic-co-glycolic acid)/xylitol nanoparticle

The PLGA/xylitol nanoparticles were made using a solvent evaporation method. Their ingredients were poly(lactic acid) PLGA 0.3% (50:50) (China), poly(vinyl alcohol) (PVA), tween-20, dimethyl sulfoxide (DMSO), and water. Several xylitol concentrations (Bloomingdale, Illinois) (5%, 7.5%, 10%, 15%, and 20% w/w) were used to create the PLGA/xylitol nanoparticles. Distilled water was used to dissolve the xylitol and surfactants, whereas acetone was used to dissolve the PLGA. Once the aqueous solution was sonicated and the organic phase was added drop by drop, it was evaporated in a rotary evaporator for two hours at 40°C. After concentrating the nanoparticles, they spent 18 h in a freezer set at 80°C. For 24 h at 110°C, the nanoparticles were lyophilized in a freeze dryer (CD-2820, China).[28] This measurement was made in University of Technology, Department of Nano Science.

Identification of nanoparticles

X-ray diffraction pattern analysis

X-ray diffraction (XRD) is a common method of measurement since it can determine the material kind and phase without damaging the sample. The diffraction

Figure 1: PLGA/xylitol nanoparticles after preparation

information is revealed when the incident beam scatters off the material at a specific angle. X-ray analysis was used to characterize the resulting nanoparticles after they were dried and dropped from suspension onto glass slides. Cu Kα (1.54 eV) at a 2 angle (10°–80°) was used as the X-ray radiation source.[29] XRD measurement was carried out in the Nanoscience Laboratory at the University of Technology.

Filed emission scanning electron microscopy

The filed emission scanning electron microscopy (FESEM) is an electron microscope that creates surface images by raster-scanning the object with a high-energy electron beam. Use of electron emitters generated by a field emission gun. These types of electron emitters can emit up to a thousand times more electrons than a tungsten filament. However, very higher vacuum levels were required. After the electron beam exits the electron gun, metal apertures and magnetic lenses are utilized to confine and focus it into a thin, monochromatic beam. Detectors of each type of electron are afterward installed in microscopes that gather signals to show an image and microstructure of nanomaterials. In-Lens FESEM gives topographical information at magnifications between 250× and 1,000,000×, with a depth of field that is practically limitless. In-lens FESEM creates images that are sharper and less electrostatically deformed than SEM[30]

The antimicrobial effects of poly(lactic-co-glycolic acid) /xylitol nanoparticles on *Streptococcus mutans and Candida albicans*

The sensitivities of Streptococcus mutans and Candida albicans to varying concentrations of poly(lactic-co-glycolic acid)/ xylitol nanoparticles suspension solutions in comparison to de-ionized water and chlorhexidine in vitro

To determine the antimicrobial effects (sensitivity test) of *S. mutans and C. Albicans* to many concentrations of PLGA/xylitol nanoparticles suspension solutions as compared to control positive. Mueller Hinton Agar (MHA) media was used and prepared according to the instructions of Hi-Media Laboratories Pvt. Ltd. Biotechnology Research, Mumbai.[31] Different concentrations of the nanoparticles suspension solutions were prepared (5%, 7.5%, 10%, 15%, and 20%).

Procedures

1. The MHA medium was prepared with accordance of Hi-Media's instructions by dissolving 35 g of the medium in one liter of de-ionized water. After being completely dissolved by boiling, then autoclaving for 15 min at 121°C, the substance is sealed tightly and stored in a cool, dry area.
2. 25 mL of MHA medium with a pH of 7 was put into clean petri dishes and left for 24 h at room temperature.
3. Each plate was subcultured with 0.1 mL of active *S. mutans* and *C. albicans* and kept at room temperature for 20 min.
4. Four wells of similar depth and diameter (6 mm) were drilled into each agar plate; 0.1 mL of the treatment substance was introduced to each well.
5. Plates were incubated aerobically for 24 h at 37°C after being kept at room temperature for an hour. No zone indicates 100% resistance to the tested drugs.

Determination of minimum inhibitory concentration and minimum bactericidal concentrations of poly(lactic-co-glycolic acid)/xylitol nanoparticles against Streptococcus mutans and Candida albicans

To standardize the *S. mutans* and *C. albicans* inoculums, a serial dilution technique was utilized. For aseptic conditions, the procedures were performed near a burner. *Candida albicans* and *S. mutans* isolates were inoculated into 10 mL of nutrient broth with pH 7.0. *Streptococcus mutans* was incubated anaerobically in anaerobic jars containing a range of atmospheric CO_2 concentrations of approximately 5% for 18–24 h at 37°C for activation before to conducting the experiment. Before the experiment was conducted, *C. albican* was activated by aerobic incubation at 37°C for 18–24 h. Standardized bacterial and fungal broth suspensions containing 10^8 (McFarland Standard 0.5) were made.[32] In order to achieve serial dilution, 9 mL of nutritional broth is put to a test tube, followed by 1 mL of microbial suspension. From the first tube, 1 mL was transferred to the second test tube and 9 mL of nutritional broth were added to complete the initial dilution. Each tube was classed by its dilution number. After categorizing the test tubes by the number of different concentrations of PLGA/xylitol nanoparticles, 1 mL of bacterial and fungal solution (3rd dilution) was added to each tube, followed by 0.5 mL of the tested agent. The tubes were then incubated for 48 h at 37°C anaerobically and aerobically for *S. mutans* and *C. albicans*, respectively. After 48 h, the tubes were checked for turbidity; the tube with turbidity was discarded, and the tube without turbidity was determined to be the MIC. The MIC is the lowest concentration of an antimicrobial agent that inhibits microbial growth.[33,34] By subculturing the clear broth, the MBC and MFC (minimum fungicidal concentrations) were determined. MBC and MFC identified by establishing the lowest antimicrobial agents concentration that reduces the viability of the initial microorganism inoculum to 99.9%.[35]

Statistical analysis

Statistical Package for Social Research was used for descriptive analysis and presentation (SPSS version 22.0, Chicago, Illinois). Levene test for such a quantitative variable that includes the minimum, maximum, mean,

standard deviation (SD), and standard error. Using Tukey's honestly significant difference (Tukey's HSD) and Dunett'sT3 post hoc test for multiple pairwise comparisons among group. No significant difference with a *P* value more than 0.05, significant difference at a *P* value lower than 0.05.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 560 in 17/4/2022 to get this approval.

Results

X-ray diffraction analysis

Cu Kα radiation was used to measure the XRD data (1.5406 A). Figure 2 shows the XRD patterns produced by PLGA/xylitol nanoparticles and xylitol. Since that xylitol had a high degree of crystallization before being converted to nanoparticles, there was a change in the width of the beak, which is a sign of the substance's transformation into nanoparticles. Scherer's equation was used to compute the substance's crystal size.

Field emission scanning electron microscopy

The FESEM analysis is a crucial test for determining the morphology of nanoparticles that have been manufactured. The form and size of nanoparticles were depicted in Figure 3. The images depict a heterogeneity of nanoparticles with various shapes and sizes <100 nm.

Sensitivity test (agar well diffusion method) of *S. mutans and C. albicans* to many concentrations of PLGA/xylitol nanoparticles in comparison to de-ionized water (DW) and chlorohexidine (CHX), *in vitro*.

Twenty pure bacteria and candida isolates were taken from a medical laboratory in Baghdad hospital and diagnosed using morphological characteristics, biochemical tests, and the VITEK 2 device. They were maintained in the fridge in nutritional agar until needed for the experiment. The agar well diffusion method was used to find the sensitivities of. *mutans* and *C. albicans* to various concentrations of PLGA xylitol nanoparticle suspension solutions as shown in Figures 4 and 5. The capacity of PLGA/xylitol nanoparticles to inhibit microbial species was investigated in this work. The results showed that nanoparticles were more effective in inhibiting *S. mutans* as the diameter of inhibition grew from 5.400 ± 3.627 to 14.840 ± 3.607 mm, with a corresponding increase in nanoparticle concentration from 5% to 20%. Except for concentration 5%, the mean values of inhibition zones

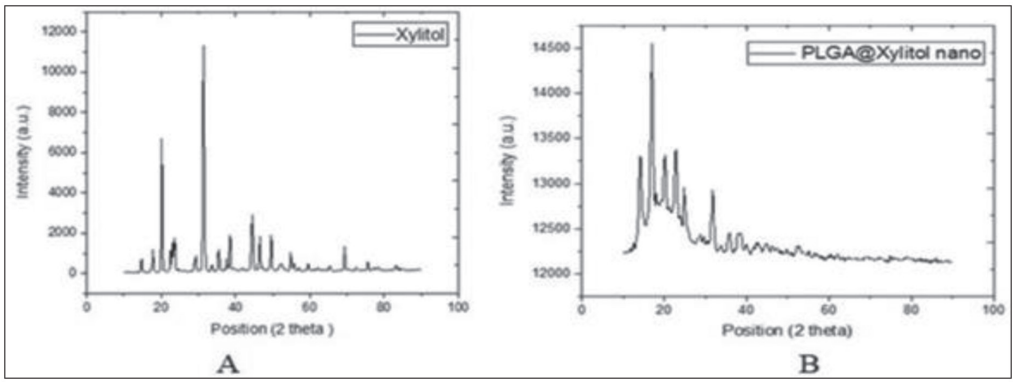

Figure 2: The XRD pattern: (A) The XRD pattern of xylitol, (B) The XRD pattern of PLGA/xylitol nanoparticles

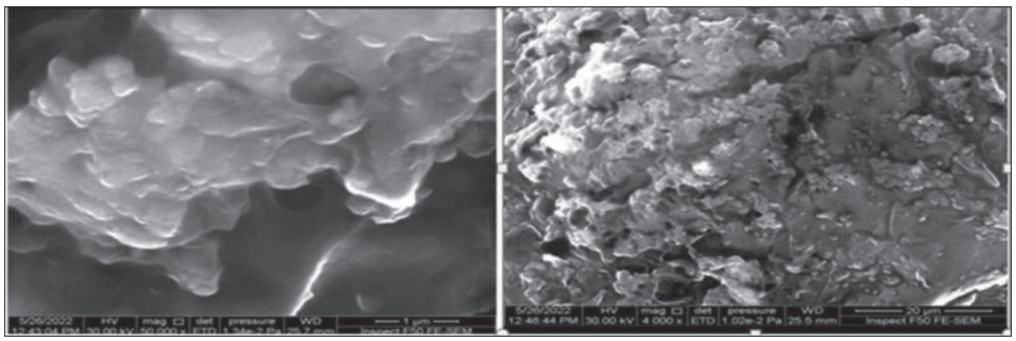

Figure 3: FESEM of PLGA/xylitol nanoparticles

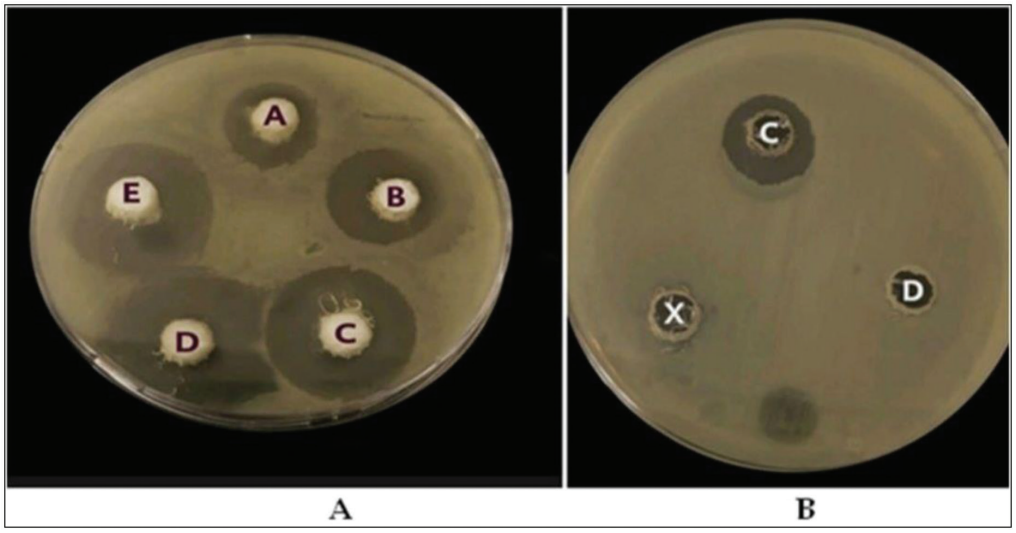

Figure 4: (A) Sensitivity of *Streptococcus mutans* to different concentrations of PLGA/xylitol nanoparticles (A = 5%, B = 7.5%, C =10%, D = 15%, and E = 20%). (B) Sensitivity of *Streptococcus mutans* to Chlorohexidine

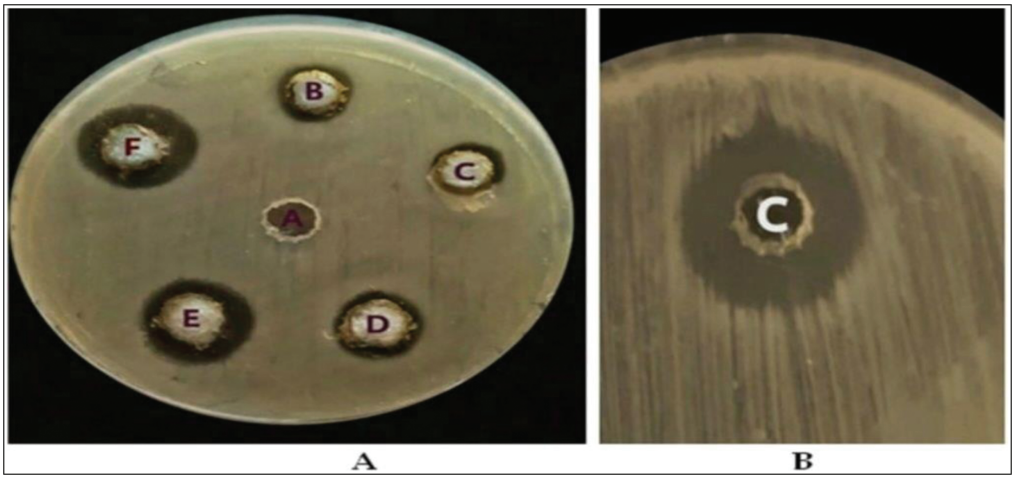

Figure 5: (A) Sensitivity of *Candida albicans* to different concentrations of PLGA/xylitol nanoparticles (A = DW, B = 5%, C = 7.5%, D = 10%, E = 15%, and F = 20%). (B) Sensitivity of *C. albicans* to Chlorohexidine

Table 1: Descriptive and statistical test of diameter of inhibition zone for *S. mutans* between groups

Groups	Mean	±SD	±SE	Minimum	Maximum	*F*	*P* value
5%	5.400	3.627	1.147	1.000	11.000	7.752	0.000015
7.5%	7.500	5.083	1.607	2.000	16.000		Sig.
10%	9.500	5.735	1.814	3.000	18.000		
15%	13.850	3.606	1.140	9.000	20.000		
20%	14.840	3.607	1.141	10.000	21.000		
0.2%CHX	7.200	3.938	1.245	2.000	14.000		
DW	0	0	0	0	0		

Levene test = 1.083

of all nanoparticle concentrations are greater than CHX 0.2% [Tables 1 and 2].

The nanoparticles were least effective in inhibiting *C. albicans* as the diameter of inhibition zones increased from 1.00 ± 0.00 to 3.40 ± 1.713 mm, with a corresponding increase in nanoparticle concentration from 5% to 20%. For *C. albicans* the inhibitory zones of chlorohexidine were found to be greater than all other concentrations of PLGA/xylitol nanoparticles with a statistically significant difference ($P < 0.05$) [Tables 3 and 4].

Determination of MIC and MBC of poly (lactic-co-glycolic acid)/xylitol nanoparticles against *St. mutans and C. albicans*

Many PLGA/xylitol nanoparticle solution concentrations were introduced to test tubes after they had been manufactured. Following incubation, it was discovered that there was turbidity with concentrations of 2.5%, 5%, and 10% for tubes containing *S. mutans* and 2.5%, 5%, 10%, and 15% for tubes containing *C. albicans*. This result revealed that a microbial growth occurred, so these tubes were excluded where the tube that contain PLGA/xylitol nanoparticles with concentration of 15% for *S. mutans* and 20% for *Candida* lack of the turbidity on naked eye (there is no visible growth of bacteria), so this tube was identified as the MIC [Figures 6 and 7], whereas the tube that contain nanoparticles with concentration of 20% for *S. mutans* and 25% for C. *albicans* is determined as MBC and MF,C respectively [Figures 8]

Discussion

Nanotechnology has been explored in a variety of medical application sectors.[36,37] Nanoparticles have numerous benefits due to their small particle size, which allows them to enter cells, increased drug release of active therapeutic agents, and lower MIC and MBC which increases antimicrobial activity with a smaller amount of drug.[20,38,39] As the concentration of PLGA/xylitol nanoparticles increases, the diameter of zones of inhibition of *S. mutans* and *Candida* increases. The mean values of the inhibitory zones of PLGA/xylitol nanoparticles 7.5%, 10%, 15%, and 20% (7.500 ± 5.083, 9.500 ± 5.735, 13.850 ± 3.606, and 14.840 ± 3.607) for *S. mutams* were greater than CHX 0.2% (7.200 ± 3.938). The diameter of inhibitory zones of PLGA/xylitol nanoparticles 15%, 20% was found to be greater than that of chlorohexidine 0.2% with statistically significant difference ($P < 0.05$), whereas for Candida, the mean values of inhibitory zones for all concentrations (1.000 ± 0.000, 1.100 ± 0.211, 1.400 ± 0.516, 2.600 ± 1.430, and 3.400 ± 1.713) are still lower than CHX 0.2% (7.600 ± 2.591). This may occur as a result of *C. albicans* infection drug resistance.[40] De-ionized water possesses no antimicrobial properties. As far as we are aware, there is no existing research on the antimicrobial action of PLGA/xylitol nanoparticles on microorganism that cause dental caries with which to

Table 2: Multiple pairwise comparisons of diameter of inhibition zone for *S. mutans* between groups using Tukey's honestly significant difference (Tukey's HSD)

(I) Groups	(J) Groups	Mean difference (I-J)	*P* value
5%	7.5%	–2.100	0.887
	10%	–4.100	0.298
	15%	–8.450	**0.001**
	20%	–9.440	**0.000**
	0.2%CHX	–1.800	0.938
7.5%	10%	–2.000	0.906
	15%	–6.350	**0.022**
	20%	–7.340	**0.005**
	0.2%CHX	0.300	0.999
10%	15%	–4.350	0.238
	20%	–5.340	0.083
	0.2%CHX	2.300	0.843
15%	20%	–0.990	0.996
	0.2%CHX	6.650	**0.014**
20%	0.2%CHX	7.640	**0.003**

The *p* value are in bold black represent significant value; The *p* value in black represent no significant value.

Table 4: Multiple pairwise comparisons of diameter of inhibition zone for *Candida albicans* between group using Dunett'sT3 post hoc test

(I) Groups	(J) Groups	Mean difference (I-J)	*P* value
5%	7.5%	–0.100	0.842
	10%	–0.400	0.325
	15%	–1.600	0.070
	20%	–2.400	**0.020**
	0.2%CHX	–6.600	**0.000**
7.5%	10%	–0.300	0.736
	15%	–1.500	0.098
	20%	–2.300	**0.025**
	0.2%CHX	–6.500	**0.000**
10%	15%	–1.200	0.285
	20%	–2.000	0.058
	0.2%CHX	–6.200	**0.000**
15%	20%	–0.800	0.978
	0.2%CHX	–5.000	**0.001**
20%	0.2%CHX	–4.200	**0.008**

The *p* value are in bold black represent significant value; The *p* value in black represent no significant value.

Table 3: Descriptive and statistical test of diameter of inhibition zone for *C. albican* between groups

Groups	Mean	±SD	±SE	Minimum	Maximum	F	P value
5%	1.000	.000	.000	1.000	1.000	31.515	0.000
7.5%	1.100	.211	.067	1.000	1.500		
10%	1.400	.516	.163	1.000	2.000		
15%	2.600	1.430	.452	1.000	4.000		
20%	3.400	1.713	.542	1.000	5.000		
0.2%CHX	7.600	2.591	.819	4.000	12.000		
DW	0	0	0	0	0		

Levene test = 9.906, *P* value = 0.000 Sig.

compare the results of this work. However, there is the previous research on xylitol. can compare with it.

Research proved xylitol's antibacterial action on streptococci mutans.[41,42] Hajiahmadi *et al*. [43] showed that *S. mutans* is only inhibited by xylitol in high concentrations, with a mean diameter of inhibition zones of 5.84 ± 0.07 after 24 h. The antifungal effect of xylitol on *candida albicans* is controversial. Vishalini *et al*.[44] reported that at all concentrations, xylitol inhibited *C. albicans*. Chan *et al*. [42] demonstrated that the dose-dependent inhibitory effects of xylitol on *C. albicans* biofilm were ineffective. Mota *et al*.[45] demonstrated that neither 10% nor 20% xylitol exhibited antifungal activity against *C. albicans*. The concentrations of 15% and 20% of PLGA/xylitol nanoparticles on *S. mutans* and *C. albicans,* respectively, were identified as the MIC due to the lack of turbidity (there is no visible growth of bacteria), which could be explained by the increase in concentration of the nanoparticles that inhibit microorganisms growth. The suspension solution of PLGA/xylitol nanoparticles was reported to be bacteriostatic and bactericidal against *S. mutans* and *C. albicans*.

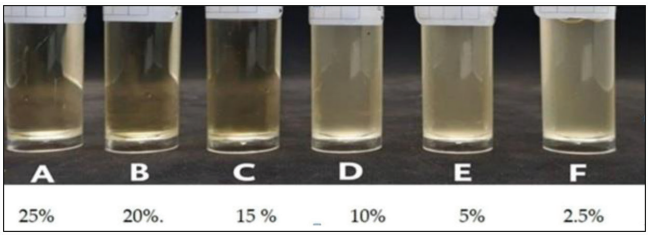

Figure 6: Minimum inhibitory concentration (MIC) of *Streptococcus mutans*. a,b,c,d,e, and f, are tubes containing different concentrations of PLGA/xylitol nanoparticle solution

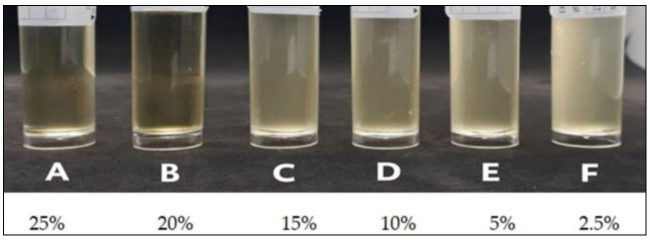

Figure 7: Minimum inhibitory concentration (MIC) of *Candida albicans*. a,b,c,d,e, and f, are tubes containing different concentrations of PLGA/xylitol nanoparticle solution

The antimicrobial effect of PLGA/xylitol nanoparticles is due to the xylitol's ability to inactivate *S. mutans* and *C. albicans*, as well as inhibit acids and polysaccharides secreted by plaque.[26,27] The mechanisms by which xylitol inhibits the growth of *S. mutans*. First, xylitol is difficult to ferment for plaque microorganisms, and the inactivity of other microorganisms balances the pH from decreasing even if some microbes are able to ferment xylitol. Secondly, the phosphoenol pyruvate phosphotransferase system converts xylitol within the cells of *S. mutans* to xylitol-5-phosphate. This prevents the formation of acid. Thirdly, some *S. mutans* develop xylitol resistance. These strains are less virulent in the mouth. Fourthly, xylitol raises the levels of amino acids and ammonia in plaque, so balancing the acidity of plaque-secreted acids.[46] The drug-loaded PLGA nanoparticles provide a greater photodynamic effect and inhibit *S. mutans* and *C. albicans* growth significantly[47,48] By incorporating xylitol into PLGA nanoparticles led to a reduction in particle size, an increase in surface area, and a promotion of xylitol's antibiofilm action.[28,49]

The synergistic effects of xylitol and PLGA are greater than the individual effects of xylitol and PLGA. The antimicrobial activity of this nanoparticles against others microorganisms causing dental caries requires further investigation.

Conclusion

The results of the current study revealed that PLGA/xylitol nanoparticles suspension solution have antimicrobial action against *S. mutans and C. albicans.* Its impact on

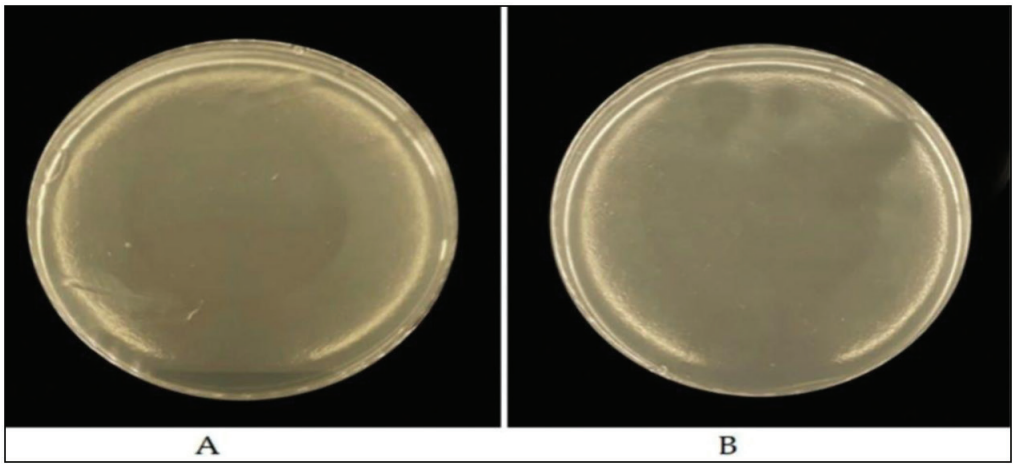

Figure 8: (A) MBC for *Streptococcus mutans*; (B) MFC for *Candida*

C. albicans is much lower. Combination of the xylitol with PLGA nanoparticles shows successful antimicrobial agent and can be used as a way of preventing dental caries.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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