



Formulation and evaluation of dental gel of *Curcuma longa* and *Phyllanthus emblica* loaded Silica nanocomposite as dental plaque inhibitor

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Abstract

The current research aimed to formulate a dental gel with an antibacterial action against *Streptococcus mutans* (the predominant cause of dental plaques) and a gel with antiplaque action by dissolution of plaque dextran. Ethanolic extracts of two medicinal plants *Phyllanthus emblica* and *Curcuma longa* were prepared and loaded onto silica nanoparticles synthesized from rice husk to obtain a silica-plant extract nanocomposite. The latter was analysed for their antibacterial action against *Streptococcus mutans* by agar well diffusion methods and plaque dissolution properties by phenol sulphuric acid methods *in vitro*. Finally, a dental gel with antibacterial and antiplaque effects was formulated using the above plant extracts, silica nanoparticles, and chitosan as key ingredients. The zone of inhibition of different components of the formulated gel indicated that individual components of *Curcuma longa*, and *Phyllanthus emblica* gave promising antibacterial activity against *Streptococcus mutans* as compared to the chloramphenicol and an increase in antibacterial role was observed in the extract combinations, with silica nanoparticle-loaded extracts giving the best activity. The percentage of dissolution of dextran was found to be higher in the silica-incorporated dental formulation, and the release of dextran was found to increase in a time-dependent manner of 70.321 mg% at 15 minutes. The formulation was noted for its antibacterial, plaque dissolution and ideal gel properties to be a suitable dental gel for plaque control. To our knowledge, this is the first report on a dental formulation gel with both antibacterial and plaque dissolution properties.

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Keywords: Dental plaque, dental gel, antibacterial, anti-plaque, *Phyllanthus emblica*, *Curcuma longa*

1.Introduction

Dental plaque consists of extracellular matrix and microorganisms, especially *Streptococcus mutans* [1], anaerobic bacteria such as *Actinobacteria*, *Fusobacterium* and sometimes a combination of various microbes [2, 3]. Plaque build-up may lead to the formation of calculus and many chronic conditions, such as gingivitis and periodontitis. Research scientists discovered that untreated dental plaque increases the risk of developing

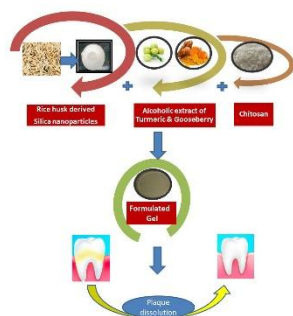
cardiovascular diseases such as atherosclerosis, myocardial infarction, etc.[4]. A close link is noted between oral health and the prevention of chronic heart diseases across different populations of people across the globe [5, 6]. It is also noted that various respiratory disease pathogens are found to be associated with dental plaques in chronic lung patients [7]. The microbiome associated with dental plaques revealed that almost 1,372 operational taxonomic units (OTUs) were found in them, which determined the health as well as disease condition of a person [6]. Thus, dental plaques and chronic diseases are closely linked, and prevention of dental plaques becomes an essential strategy to prevent chronic disease manifestations [8]. As per a study conducted by National Health Insurance (NHI) of Taiwan, almost 55.69% of dental use in Taiwan was related to dental caries treatment, an outcome of prolonged dental plaque occurrence [9].

Plaque removal, control and prevention are usually done mechanically by proper oral hygienic methods and chemically using chlorhexidine-gluconate base antiseptic or oral disinfectants [10]. A close look at dental plaque treatment has led to the development of various dental implants, laser-based instruments and technologies to address the problem of dental caries [11, 12]. Different hydrogels with antibacterial or remineralisation and tissue engineering properties have been developed to find practical solutions to dental caries and plaques [13]. The use of liquid carriers of various nanoparticles with antibacterial activity against oral pathogens has also been attempted [13]. The fundamental strategy of different preventive methods developed so far involves the formation of antibiofilm agents, which prevent microbial growth and film formation on teeth [14]. Treating dental caries also involves various antimicrobial agents such as beta-lactam drugs, broad-spectrum tetracyclines, macrolides, chemicals such as fluoride, quaternary ammonium salts, and antimicrobial peptides [15]. However, excessive use of these drugs may lead to several health problems and result in the development of resistant bacterial strains [16], thereby demanding alternate methods to deal with drug resistance.

Various natural plants such as *Phyllanthus emblica* and *Curcuma longa* are very commonly available plants which are having anti-plaque activity because of their antibacterial activity against the cariogenic bacteria, stimulation of salivary secretion and anti-inflammatory activity while also reducing the chance of the development of resistant bacterial strains [17, 18].

Curcumin has anti-inflammatory and antibacterial activity, especially against *Streptococcus mutans* [19, 20]. Studies showed that curcumin alone or in combination with other anticancer agents, has potential anticancer effects [21, 22]. Ethanolic extract of *Phyllanthus emblica* is very effective against cariogenic bacteria, especially *Streptococcus mutans* [23]. Being a rich source of vitamin C and other nutrients like pectin, calcium, iron, and phosphorous; *Phyllanthus emblica* is a potent antioxidant, antibacterial, antiviral and hypolipidemic [24, 25].

Regardless of their medicinal properties, natural products also face problems associated with less permeation across the teeth tissue, affecting their efficacy. The slow release of these compounds and non-permeability against teeth can be overcome by using nanoparticles as drug-delivering agents. Nanoparticles owing to their small size, penetrate regions that may be inaccessible to other drug delivery systems, such as periodontal pocket areas below the gum line. Nanoparticles enable the encapsulated molecule to retain its biological activity from the production step to the final release. Nanoparticles provide several advantages compared to other targeted drug delivery systems, including high dispersibility, controlled release rate and increased stability. The current research paper attempts to combine the therapeutic potential of *Phyllanthus emblica* and curcumin to control and prevent the causative agents of dental plaque. Silica-based nanoparticles also serve as ideal drug delivery agents [26]. Thus, a formulation of a hydrogel is done using the combinations of *Curcuma longa* and *Phyllanthus emblica* and silica nanoparticles as effective dental plaque inhibitors. Silica-based nanoparticles derived from rice husk have more importance because rice husk is the biowaste and can be converted into useful silica-based nanoparticles because of its high silica content.



2. Materials and Methods

2.1. Isolation and Identification of Microorganism causing dental plaques

The bacterial culture of *Streptococcus mutans* was isolated from patients with dental caries on Nutrient agar plates after incubation at 37°C for 48 hours to obtain well-defined colonies. The distinct colonies were further identified by gram staining, biochemical properties and molecular methods using 16S rDNA typing methods as published protocols [27].

2.2. Preparation of Plant Extracts

The fruits of *Phyllanthus emblica* and rhizomes of *Curcuma longa* isolated from Kochi, India, were washed and chopped into small pieces, sundried for ten days and ground into fine powder. Plant extracts were extracted in 95% ethanol by the process of maceration, kept for three days, followed by filtration to obtain the extract [28]. The concentrated extract was obtained using a rotary evaporator set at a temperature of 60°C to allow solvent evaporation. The concentrated samples were dissolved in DMSO at a 100 mg/ml concentration for further studies.

2.3. Synthesis and Characterisation of silica nanoparticle from rice husk

The synthesis of nano-silica was done using pure silica isolated from rice husk ash through a series of steps. Rice husk was washed with distilled water and burned at 700°C for six hours to obtain rice husk ash (RHA). Rice husk ash (10 grams) was primarily treated with 80 ml 2.5N sodium hydroxide solution, boiled for 3 hours, followed by filtration and washed in boiling distilled water. The filtrate so obtained was cooled to room temperature, underwent sequential acidification and alkalisation by treatment with 5N H₂SO₄ until pH 2, followed by treatment with NH₄OH for 3.5 hours at a pH of 8.5 to yield a filtrate of pure silica which was dried at 120°C for 12 h.

Pure silica was extracted by refluxing with 6 N HCl for four hours and then washed repeatedly using deionised water to make it acid-free. It was then dissolved in 2.5 N NaOH by continuous stirring for 10 h on a magnetic stirrer, and then concentrated H₂SO₄ was added to adjust pH in the range of 7.5-8.5. The precipitated silica was washed repeatedly with warm double distilled water until the filtrate became completely alkali-free. The washing process continued by deionised water repeatedly and dried at 50°C for 48 h in the oven.

The synthesised silica nanoparticle was analysed using a Perkin-Elmer UV-VIS spectrophotometer, Lambda-19 to know the kinetic behaviour of nanoparticles using a scanning range of 200-600 nm. FTIR Analysis of the sample was done by KBr pellet technique using Perkin Elmer FTIR Spectrum RX1 ATR. The crystallinity of the particle was determined by X-ray diffraction (XRD) Shimadzu, Japan XRD – 7000. The structural analysis of the nanoparticles was done using Scanning Electron Microscopy (Carl Zeiss, Germany).

2.4. Formulation of plant extract –silica nanocomposite and Antimicrobial Assay

The formulation of the plant extract and silica nanoparticles was done at a concentration of 20 mg of silica nanoparticles at 100 ml of plant extract. Primary screening of antimicrobial potential of plant extracts [*Phyllanthus emblica* (PE), *Curcuma longa* (CL)] and silica nanoparticles, both individually and in combination, was done by agar well diffusion method against the bacterial pathogen (*Streptococcus mutans*), turbidity equal to 0.5 Mc Farland (2×10⁸ CFU/ml), spread with a sterile cotton swab on Muller Hinton Agar. To summarise, 100µl each of the extracts was added to wells (6mm) formed by a Cork borer on the MHA agar. The plates were incubated at a suitable temperature for 24 – 48 hours. The zone of inhibition was measured, and the agar disc diffusion method was used for antibacterial assay [29]. The standard antibiotic, chloramphenicol (25 µg/ml), was used as a positive control.

2.5. Plaque dissolution Assay

Plaque dissolution properties of different components used in the antimicrobial assay were done as per standard protocols [30]. A pool of dental plaque was collected separately using a Columbia scaler in a test tube containing 2 ml of chilled glass distilled water, was sedimented by cold centrifugation at 5000 rpm for 5 minutes and preserved at -20°C temperature. The collected plaque samples were taken in separate test tubes (100 mg each), treated with different extracts (1ml each) and dental gel formulation (0.1 g each), vortexed and kept for dissolution for 15- 30 minutes. The supernatant fluid obtained post-centrifugation at 5000 rpm for 10 minutes was analysed in triplicates for dissolved dextran content by spectrophotometric analysis at 480 nm against standard concentrations of dextran and proper controls by phenol sulphuric acid method [30]. Pure dextran, molecular weight (MW) 10,000 (REF – RM736-5G) was obtained, and various standard solutions of 10 mg%, 20 mg%, 30 mg%, 40mg%, 50mg% and 60 mg% of standard pure dextran were prepared in glass distilled water.

2.6. Formulation and characterisation of gel based on silica nanoparticle-plant extract

Gels were prepared by the cold mechanical method using a required quantity of polymer weighed, sprinkled slowly on the surface with purified water for 1.5 hrs., followed by continuously stirring using a magnetic stirrer, till the polymer is soaked in the water. The other ingredients were added during continuous stirring as per Table 1. Finally the prepared silica nanoparticles were added to the gel with continuous stirring till it was completely dispersed in the gel. Two formulations of silica nanoparticle incorporated gels were prepared by using polymer chitosan and carbopol, the composition of each gel as explained in Table 1 and stored in a dark and cool place for further analysis.

Table 1 Composition of gel prepared using plant extract- nanocomposites

Gel A	Gel B
Carbopol : 2 g	Chitosan 2 g
Glycerol : 2 g	Glycerol : 2 g
Glacial acetic acid : 1.5 ml	Glacial acetic acid : 1.5 ml
Plant extract incorporated silica nanoparticle : (0.02 g nanoparticle /100 ml of extract)	Plant extract incorporated silica nanoparticle: (0.02 g nanoparticle /100 ml of extract)
Water up to 100 g	Water up to 100 g

2.7. Characterisation of formulated dental gel

The prepared gel was characterised by its transparency, smoothness, relative density, spreadability, pH, extrudability, and viscosity as per standard procedures. The antibacterial activity and anti-plaque assay of the formulated gel were done as described in the respective sections above against suitable controls.

3. Results and Discussion

3.1. Isolation and identification of Microorganism causing dental plaques

As per the statistics of the World Health Organisation dental caries accounts for permanent teeth decay in 2 million people globally and almost 514 million children face primary teeth caries (<https://www.who.int/publications/i/item/9789240061484>). Though a wide range of microbes, including facultative and obligate anaerobic microbes, can contribute to dental caries, the most predominant cause of dental caries is *Streptococcus mutans* [31]. These bacteria on development of plaque create a holistic niche for the survival and replication of many acidogenic and aciduric bacteria [32]. *Streptococcus mutans*, the oral pathogen, has also been associated with endocarditis and cardiac diseases [33]. Thus, it is often wise to prevent dental caries rather than let the microbe lead one to more complex situations of cardiac diseases.

The bacteria *Streptococcus* isolated in the current research work formed gram positive cocci arranged as straight chains under gram staining. The 1.5 kb amplicon obtained after 16S rDNA of the isolate was sequenced, submitted to NCBI database with accession number OR563799. The 16S rDNA sequence showed 100% similarity to *Streptococcus mutans* strain ATCC 25175 on BLAST with the NCBI database. *Streptococcus mutans* is found as normal oral flora and is capable of causing biofilm in teeth [34]. The development of dental caries in susceptible hosts is an aftermath of solidification of *Streptococcus biofilms* over time on teeth accompanied with simultaneous production of lactic acid in presence of fermentable sugars in the oral cavity [35]. This bacterium is capable of producing high amounts of acids on the fermentation of simple sugars such as sucrose and fructose on tooth surfaces as food debris, resulting in the damage of hard tooth structure [1]. As per studies down-regulation of virulence genes responsible for Streptococcal adherence, biofilm formation, extracellular polysaccharide synthesis and acid formation could be effective modes to control dental caries [36].

3.2. Synthesis and characterisation of silica nanoparticles

Silica nanoparticles are considered as versatile tools in combating bacterial infections as agents for targeted drug delivery possessing properties such as biocompatibility, high drug loading capacity, and retention abilities [37]. The synthesis from rice husk also have an additional property of converting a biowaste to a biomedically useful material [38]. The synthesized silica nanoparticles from rice husk ash were characterised by UV- Vis spectroscopy to observe a peak at 297 nm, indicating the formation of nanosized particles. However, standard silica analysis failed to show any such peak formation indicating that the new peak was a result of the nanosilica

formed from rice husk. The individual as well as combinatorial use of silica materials/nanocomposites has wide application in biomedicine to combat antimicrobial resistance and tissue engineering [39].

The major chemical groups present in silica nanoparticles were identified by FTIR spectral analysis with the band at 468 cm⁻¹ corresponding to Si–O rocking vibration, as shown in (Fig 2a). The band around 804 cm⁻¹ corresponds to Si-O bending vibration, 1466.84 cm⁻¹ corresponds to Si-OH bending vibration, the band at 1103 cm⁻¹ corresponds to the asymmetric stretching vibration of the Si-O-Si band, and the band around 2924 cm⁻¹ corresponds to Si-OH stretching vibration. The XRD pattern of silica nanoparticles synthesised from rice husk exhibited beaks between 22 ° and 23° (2 Θ) values and exhibited a crystal size of 22.45 nm (fig 2b). Typical silica characteristic is observed with broad peaks between 22 ° and 23° (2 Θ). This indicates that samples are crystalline with a crystal size of 22.45 nm. The SEM analysis revealed the formation of nanoparticles of a size less than 1 μ m (Fig 2c).

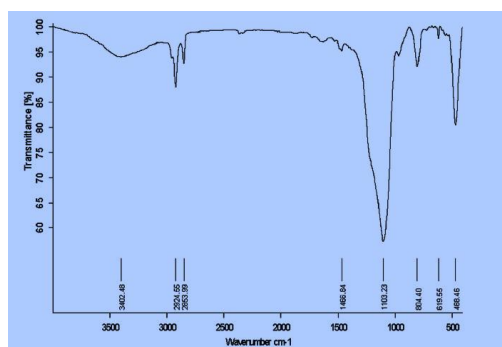


Figure 2a: FTIR

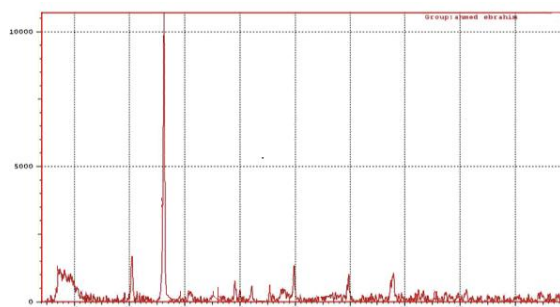


Figure 2b: XRD

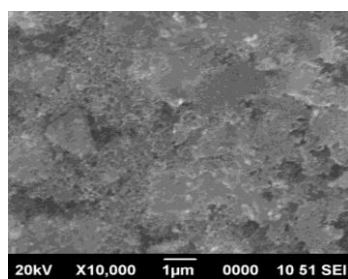


Figure 2c: SEM analysis

3.3. Formulation and characterisation of plant extract- silica nanocomposite gel

The dental gels are formulated by carbopol and chitosan with *Phyllanthus emblica*, and *Curcuma longa* loaded silica nanoparticles (**Fig 2**) were observed to be clear and have a uniform consistency. Table 4 shows the rheological characteristics of the gels. Gel B has more viscosity than gel A. The gels showed pseudoplastic flow with variable thixotropic behaviour. Gel B has more spreadability than gel A. Gel B has better extrudability than gel A. Overall, the gel prepared with chitosan is better than the gel prepared with carbopol.

The spreadability of formulated dental gel was 18.75 gcm/sec (Table 2). During the accelerated stability studies, the appearance was clear, no significant variation in pH was observed, and spreadability just went to 17.95 after three months (Table 3). The pH was also maintained throughout the study, which was found to be 6.96 to 6.98 (Table 3).

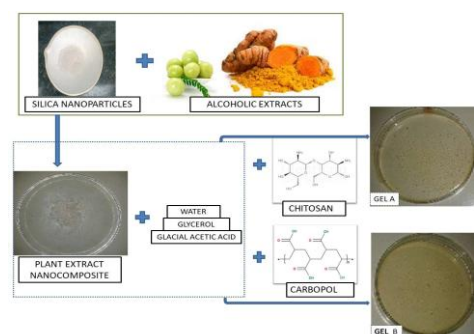


Fig 2. Scheme for the formulation of dental gel

Table 2 Physico-chemical and rheological properties of formulated dental gel

S.No.	Property	Gel A	Gel B
1	Colour	Yellowish white	Yellowish white
2	Appearance	Homogenous	Homogenous
3	Transparency	Translucent	Translucent
4	Smoothness	Smooth	Smooth
5	pH	6.79 ± 0.052	6.98 ± 0.054
6	Spreadability	17.89± 0.251	18.75 ±0.282
7	Viscosity	2320	2459
8	Extrudability	19.15± 0.075	20.70 ± 0.135

Table 3 Stability studies and physicochemical characteristics of formulated dental gel over 3 months

Stability Testing conditions	Colour	Appearance	Spreadability	pH
25°C ± 2°C/ 60% ± 5% RH (3rd months)	Yellowish white	Homogenous	18.40	6.98
30°C ± 2°C/ 65% ± 5% RH (3rd months)	Yellowish white	Homogenous	18.34	6.97
40°C ± 2°C/ 75% ± 5% RH (3rd months)	Yellowish white	Homogenous	17.95	6.96

3.4. Antimicrobial Assay of plant extract- silica nanocomposite gel formulations

Phyllanthus emblica is a fruit with polyphenolic compounds with antibacterial, antioxidant properties and wound-healing properties that could induce saliva secretion, regulate the oral microflora, and prevent oral cancers [17]. The role of *Curcuma longa* in oral health, anticancer effects, and prevention of periodontitis is also well studied [40]. The plant extracts of *Curcuma longa* and *Phyllanthus emblica* were found to be antibacterial against *Streptococcus mutans* as per the above study and a combinatorial use also found a complementary role in the antibacterial action.

The zone of inhibition of different components of the formulated gel indicated that individual components of *Curcuma longa*, *Phyllanthus emblica* gave promising antibacterial activity against *Streptococcus mutans* as compared to the chloramphenicol standard. However, an increase in antibacterial role was observed in the extract combinations, with silica nanoparticle-loaded extracts giving the best activity as shown in Table 4. This increase in the activity could be attributed to the effective diffusion and permeability of nanoparticle-loaded extracts into the medium. This substantiates the benefit of incorporating a nanosized ingredient into the formulation, thereby increasing the extent of permeability of the bioactive compounds of the extracts. The ability of these plant extracts to boost the immunity of people is also an added advantage to their frequent use [41, 42].

Table 4 Antibacterial activity of plant extracts and formulated dental gel against *Streptococcus mutans* with suitable controls. *Values in triplicates are expressed as mean ± standard deviation

S.No.	Treatment	Zone of inhibition in mm*
1	Ethanollic extract of <i>Curcuma longa</i>	21.3± 0.152
2	Ethanollic extract of <i>Phyllanthus emblica</i>	22.2 ± 0.1
3	Mixture of Ethanollic extract of <i>Curcuma longa</i> and <i>Phyllanthus emblica</i> (1: 1)	23.3 ± 0.125
4	Plant extract loaded silica nanoparticle (0.2mg/ml)	24.3 ± 0.152
5	Silica control	Nil
6	Chloramphenicol positive control	24.3 ± 0.057
7	Gel A	24.5± 0.057
8	Gel B	24.6 ± 0.134

3.5. Plaque dissolution Assay of plant extract- silica nanocomposite gel formulations

The aetiology of dental caries reveals that when 24-hour-old plaques are soft and removable, plaques after a period of 72 hours, get hardened and are difficult to remove [43], thereby implying the adoption of proper dental health practices on a daily basis. As per studies, proper dental brushing, as well as the use of natural

product-based toothpaste, have an immense role in the prevention of dental plaques [44]. The necessity of dental plaque removal has become so relevant that the development of personalised 3D printed plaque removal strategies for the aged with effectiveness between a manual toothbrush and oral rinsing techniques has also been explored [45].

Probiotic formulations, as well as microbes such as *Lactobacillus paracasei* have been found to inhibit the dental biofilms and plaque formation in teeth and dental braces [46, 47]. Mouthwash based on 0.1% cymenol with a short-term anti-plaque effect is also a proven remedy to prevent plaques, as per *in situ* studies [48]. Many chemicals, such as triclosan and fluorides, are effective against oral bacteria but also cautioned for their adverse effects.

The necessary property of an ideal dental caries-preventing agent is its antibacterial role against *Streptococcus mutans* to prevent plaque formation, as well as its ability to dissolve the plaques formed. The current research work mainly addressed the above two characteristics and resulted in the development of an anti-dental-caries gel. In this research, efforts are made to develop an oral formulation which is having plaque dissolution and antibacterial activity against oral pathogens and has minimal side effects. Though the antibacterial effects of *Curcuma longa* and *Phyllanthus emblica* plant extracts have been widely studied, not much work has been done on their plaque dissolution effects. As per results compared to standard graphs, the percentage dissolution of dextran released from glass distilled water is 4.63 mg%, of *Phyllanthus emblica* is 44.5 mg%, of *Curcuma longa* is 39.1 mg% and of the mixture of extracts shows better dissolution of plaque dextran is 66.1mg% as per table 5.

It was noted in the above study that the extracts of *Curcuma longa* and *Phyllanthus emblica* exhibited a plaque dissolution effect in a time-dependent manner. Similarly, silica nanoparticles alone showed a very small dissolution of plaque dextran. The percentage of dissolution of dextran was found to be higher in the silica incorporated dental formulation, and the release of dextran was found to increase in a time-dependent manner of 70.321 mg% at 15 minutes and 77.42 mg% at 30 minutes. This result shows that the prepared dental gels containing plant extract-loaded nano-silica composite have promising dental plaque dissolution characteristics. The carpool-based gel had a lesser effect on plaque dissolution than chitosan-based gel, as per Table 4.

Silica nanoparticles are ideal drug delivery agents that could be used in oral treatments, and it was also evident in the dental formulation made in the above study [49]. The use of silica nanoparticle-loaded curcumin inside dental implant fixtures owing to their antibacterial action has also been explored [50]. The effective concentration of silica nanoparticles in the gel formulation was found to be 200µg/g of the gel, and a sample volume of 0.1 g was used in each dental plaque assay, thereby reducing the effective exposure concentration to 20 µg.

A close look at the plaque dissolution studies indicates that silica nanoparticles individually did not exhibit any plaque dissolution or antibacterial action; however, they served as an effective carrying agent for the plant extracts used in the formulation. Silica nanoparticles are currently used in dental fillers owing to their biocompatibility and low cost [49]. To the best of our knowledge, this is the first report on a dental formulation gel with both antibacterial and plaque dissolution properties within a time of 15 minutes. In a study involving collagen-coated hydroxyapatite, it was noted that a 3-minute exposure time could reduce plaque biofilm development within 12-hour intervals. However, the dental formulation developed in the study is superior as it aids in the dissolution of dextran from a plaque in a time-dependent manner.

Table 5 Estimation of plaque dissolution properties of various extracts and formulated dental gel

Treatment	Exposure to plaques for 15 minutes		Exposure to plaques for 30 minutes	
	Absorbance at 480 nm	% dissolution of dextran	Absorbance At 480 nm	% dissolution of dextran
Extract of <i>Curcuma longa</i>	0.41±0.02	35.5	0.44 ±0.02	39.1
Extract of <i>Phyllanthus emblica</i>	0.53±0.13	43.1	0.54±0.13	44.5
Mixture of extracts	0.62 ±0.14	66.1	0.68±0.17	67.5
Silica nanoparticles	0.01±0.02	1.1	0.01±0.03	1.1
Dental gels containing mixture of extracts loaded silica nanoparticles (Gel A)	0.51±0.14	42.0	0.51±0.13	42.0
Dental gels containing mixture of extracts loaded silica nanoparticles (Gel B)	0.80±0.17	70.32	0.88±0.21	77.42
Control	0.06±0.15	4.6	0.07 ±0.10	4.7

4. Conclusion

The present study aimed the development of a safe and effective formulation for treating dental plaques with minimal side effects. The antibacterial activity of *Phyllanthus emblica* and *Curcuma longa* is effectively used in this formulation, and silica nanoparticles are used as carrier for the plant extract with the intention of better targeted action. Silica nanoparticles obtained from rice husk have high surface area, low cost and appreciable structure integrity. *Phyllanthus emblica* and *Curcuma longa* loaded silica nanoparticles are effectively loaded into dental gel formulation serve as ideal mode for topical application. The two polymers chitosan and carbopol, used for the preparation of dental gels, are biocompatible and biodegradable in nature. As a whole the prepared dental gel formulation is safe, biocompatible and biodegradable in nature. The study revealed that the prepared formulation having 70 % dental plaque dissolution activity and almost same antimicrobial activity as that of marketed formulation.

Data Availability

Data will be made available on request.

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