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Oral microbial shift induced by probiotic *Bacillus coagulans* along with its clinical perspectives

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ABSTRACT

When used in adequate amounts, Probiotics are considered to beneficially affect host health in many respects. *Bacillus coagulans*, with its probiotic characteristics, has recently attracted the attention of many researchers and food manufacturers due to its high tolerance in extreme environments because of its spore-forming nature. Several beneficial effects of *B. coagulans* have been estimated as it exhibits properties of both the genera *Bacillus* as well as *Lactobacillus*. Recent literature has proven that *B. coagulans* has therapeutic effects on intestinal diseases including acute diarrhea, irritable bowel syndrome, antibiotic-related diarrhea, constipation, and colitis via modulation of the microbial composition, host immunity, and general metabolism. Due to the evidence supporting various probiotic effects of *B. coagulans*, the administration of many *B. coagulans* strains has been studied in the prevention and management of several oral diseases and conditions. The current review summarizes the probiotic characteristics and clinical, microbiological changes associated with the application of *B. coagulans* in oral health and diseases along with its future perspectives.

1. Introduction

The oral cavity is a source of a diversified and unique microbiome, and oral biofilm can be a contributory factor to many oral as well as systemic diseases.¹ With over 700 bacterial taxa, the oral microbiota is extremely dynamic and maintains equilibrium despite its continuum with the outer environment.² Dental plaque, is a typical example of an oral biofilm, a contributor to most oral conditions.² The predominant ecological and environmental factors that govern the profile of an oral biofilm which in turn helps to delineate the ideal treatment plan for each patient.³ Dysbiotic states in the oral biofilm driven by ecological stress convert commensal bacteria to opportunistic ones, which leads to pathogenesis.² Recently, with the completion of the Human Microbiota Program, people have become progressively aware of oral microbes but have not further evaluated oral microbiota in oral conditions like caries, periodontal disease, and oral cancer, etc.³ Evidence shows that oral microbiota is also closely related to systemic diseases, including rheumatoid arthritis (RA), adverse pregnancy outcomes, and cardiovascular disease.⁴ Therefore oral microbiota can be used as targets to prevent and treat oral and systemic diseases.⁴

Management of oral biofilm and compositional shift in oral microbiota can be done using various approaches in dentistry.⁵ Nowadays, escalated attention has been given to probiotic supplementation as a

therapeutic adjunct to improve oral health. Probiotics as defined by FAO/WHO as 'live microorganisms which, when administered in adequate amounts, confer a health benefit on the host'.⁶ The various beneficial effects of probiotics include modulation of the composition and activity of the microbiota, enhancement of epithelial barrier function, modulation of the immune system, modulation of systemic metabolic responses, and signaling via the central nervous system.⁶ *Bacillus* is the newer probiotic species now gaining attention in the field of dentistry due to its potential benefits in the field of medicine.⁷ Of these species, *Bacillus coagulans* is one of the species that generate endospores, which make it tolerant to host environments.⁷ Therefore, *B. coagulans* is highly stable in production, storage, transportation, and administration, making it a more suitable candidate for food and pharmaceutical formulations.⁷ *B. coagulans* has a long history of safe use in food and is granted Generally Recognized As Safe (GRAS) status by the Food and Drug Administration of the United States.⁷

To the best of our knowledge, there were hardly any reviews that described the clinical and microbiological effects of *B. coagulans* on oral diseases. A study in children had summarized the probiotic characteristics of *B. coagulans* including the adhesion properties, and antimicrobial abilities the study reported the ability of *B. coagulans* to reduce and inhibition of caries causing *mutans streptococci* and *lactobacilli* levels in plaque.⁸ Therefore, in this literature review, we focused on the

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probiotic characteristics of *B. coagulans* in oral health and disease prevention. along with the microbial shift associated with *B. coagulans* applications and also highlight its latest advances.

2. *Bacillus coagulans*

Bacillus species have received considerable attention nowadays in dentistry because of their economic as well as medical importance. The genus *Bacillus* has undergone considerable taxonomic changes over time.⁹ Accordingly, it will also be interesting to mention the evolutionary connections of probiotic *Bacillus* species/strains with alternative members of this genera. In this review, we are looking over the significance and approaches of *Bacillus coagulans* probiotics in oral diseases in current scenario.

2.1. Nomenclature

Bacillus genus is substantially related to *Lactobacillus* spp., the well-acclaimed probiotic candidate. Strains of *B. coagulans* have characteristics of both *Lactobacillus* and *Bacillus*, and had been previously classified into one of the genera.^{8–10} In addition to *B. coagulans*, some strains were named *Lactobacillus sporogenes* or *Bacillus sporogenes*. Still, now, some commercial products are labeled as *L. sporogenes*. *B. coagulans* was originally described in 1915 at the Iowa Agricultural Experiment Station, with regard to the coagulation of canned evaporated milk.^{9 10} *Lactobacillus sporogenes* was first isolated and described in 1933 by Horowitz-Wlassowa and Nowotol, and subsequently reclassified as *B. sporogenes*.¹⁰ More recently, studies demonstrated that *B. sporogenes* share identical features of *B. coagulans*, and thus it is currently reclassified into *B. coagulans*.⁸ Therefore, the term *B. coagulans* is used exclusively in this review.

2.2. Probiotic niches and its availability

Generally, the genus *Bacillus* is identified as a category of soil inhabitants. *Bacillus* spp. can also be isolated from varied sources including air, water, human and animal gut, and also from vegetables and food.¹¹ Based on phenotypic and genotypic characters, *Bacillus* spp. represents the most heterogeneous group.⁹ Some distinct *Bacillus* species have also been recognized as opportunistic pathogens or toxin producers in human or animal hosts. Both *Lactobacillus* and *Bacillus* share the same class, but *Bacilli* are under the phylum Firmicutes.¹⁰ It is proclaimed that the candidate probiotic should be isolated from the gut of the target population, which helps them to thrive well within the gut attributed to their probiotic perspective.⁹ But, elementary attributes of native flora for survivability are not essential for spore-former(s).⁹ It is believed that *Bacillus* spp. is not a natural inhabitant of the gut.⁹ Vegetable consumption and soil microflora contaminated raw food materials lead to intestinal tract colonization by *Bacillus*.⁹ *Bacillus* spores can survive in utmost stomach acids and tolerate bile salts and other extreme host gastrointestinal conditions.⁹ Besides, bacilli are more stable during the processing and storage of food and pharmaceutical preparations, which makes them a more suitable ingredient for oral-health promoting formulations.⁹ Thereby, in addition to human sources, *Bacillus* strains with probiotic attributes are also isolated from fermented or unfermented food sources and are commercialized in the form of a diverse range of health supplements.¹²

2.2. Biological features

Bacillus signifies a Gram-positive, rod-shaped, spore-forming, aerobic, or facultative anaerobic motile bacterium.¹³ The optimum growth temperature ranges from 35 to 50 °C.¹³ The optimum growth pH is 5.5–6.5.¹³ This bacteria ferment maltose, mannitol, raffinose, sucrose, and trehalose with the production of acid but not gas.¹³ Due to the large amount of lactic acid produced in the metabolism, *B. coagulans* is

frequently reported to cause spoilage of dairy products, vegetables, or fruits.¹⁰ The oval endospores are located at the bacterial poles of *B. coagulans*, which differs from the positions of endospores in other bacteria of the genus *Bacillus* (centrally or subterminally).¹⁴ The endospores are tolerant to heat and other harmful environmental stresses, and generally, *Bacillus* spores can germinate in the host gastrointestinal tract.¹³ The endospores of *B. coagulans* can germinate in dilute solutions of hydrochloric acid or sodium hydroxide.¹⁴ Therefore, the spores of *B. coagulans* can resist gastric acid to reach the small intestine, where they can germinate and propagate.¹⁴ The average time from oral administration to germination is 4–6 h.¹⁴ Approximately 85% of the spores reach the intestine.¹⁴ However, *B. coagulans* lacks the capability of intestinal colonization and can only temporarily reside in the intestine., but lesser known regarding the oral colonization of *Bacillus coagulans*.¹⁴ After a single oral administration, *B. coagulans* is excreted in feces for about 7 days.¹³ Therefore, in order to achieve long-term treatment, Up to date, there are 31 Genome Assembly and Annotation reports of *B. coagulans* strains on the NCBI, including some commercially important chemical-producing strains, as well as probiotic strains, for example, *B. coagulans* Unique IS-2.¹⁵ Some important enzymes produced by different *B. coagulans* strains are listed in Table 1.

2.3. Mechanism of action and oral health benefits

Probiotic strains of *B. coagulans* exert a variety of beneficial effects, including modulation of the microbial composition, alteration of immune responses and metabolism along with the production of various antibacterial products including bacteriocins and enzymes.¹⁶

2.3.1. Modulation of the quality and composition of the primitive microbiota

Although *B. coagulans* can only temporarily reside in the intestine, they can remarkably modulate the gut microbiota along with oral microbiota by increasing the number of beneficial microorganisms and counteracting or antagonizing pathogenic microorganisms.¹⁶ A strain of *B. coagulans*, BDU3, which was isolated from fermented fish, generates a distinct bacteriocin with a wide range of the antimicrobial spectrum.¹⁶ Different *B. coagulans* strains produce varying bacteriocins, the I4 strain produces the substance coagulin; ATCC 7050 produces a novel antimicrobial peptide lactosporin¹⁷; both of which showed distinct antimicrobial activity. Antifungal activity was shown by a strain of *B. coagulans* against *Fusarium* spp. *in vitro* experiments.¹⁸ A clinical investigation demonstrated that daily consumption of *B. coagulans* potentially increased the production of anti-inflammatory factors.¹⁹ In rat models, oral administration of *B. coagulans* increased the number of *Lactobacillus* colonies.²⁰ In a rat model, oral consumption of *B. coagulans* together with prebiotic inulin remarkably increased the number of lactic acid bacteria, total anaerobic bacterial count, and total aerobic bacteria, while there is a significant decrease in the number of *Enterobacteriaceae* bacteria in the intestinal tract.²¹

B. Coagulans Unique IS2 is also known to reduce caries-causing microorganisms *mutans streptococci* and *lactobacilli*, by preventing the overgrowth of these pathogenic microbes.⁸ The role of *B. Coagulans* in oral health management is progressively being acknowledged with the action mechanisms to be antagonistic activity against pathogens,

Table: 1
Products from various *B coagulans* strains.¹⁵

Strain	Product
<i>Bacillus coagulans</i> DSM 2314	Lactic acid
<i>Bacillus coagulans</i> IPE 22	β-galactosidase
<i>Bacillus coagulans</i> RCS3	α-galactosidase
<i>Bacillus coagulans</i> KM-1	α-galactosidase
<i>Bacillus coagulans</i> B49	α-amylase
<i>Bacillus coagulans</i> ZJU318	Lipase

coaggregation and growth inhibition of pathogens, production of bacteriocin and organic acid, and production of hydrogen peroxide along with interaction with oral epithelium resulting in the reduction of the pathogenicity and cariogenic potential of biofilm microbes.²² According to the results of recent studies, *B. coagulans* has been reported to have a good regulatory effect on dysbacteriosis caused by various factors.²³ *B. coagulans* can help create an anaerobic and acidic oral environment, which is not hospitable to various pathogens, thereby promoting the growth of some probiotics.²³ As facultative anaerobic bacteria, *B. coagulans* strains can consume free oxygen and reduce redox reactions.²⁴ This has been proven to be beneficial to the growth of anaerobic microorganisms such as *Lactobacillus* and *Bifidobacterium*.²¹

2.3.2. Modulation of host immunity

Immunity also appears to have a role in both innate and adaptive immune responses involved in combating oral diseases.²⁴ The metabolites of *B. coagulans* GBI-30, 6086 promoted the maturation of antigen-presenting cells *in vitro*.²³ Inactivated *B. coagulans* GBI-30, 6086 cells could activate human immune cells and alter the production of both immune activating and anti-inflammatory cytokines and chemokines.²⁴ *In vitro* experiments showed that cell walls and culture supernatants of *B. coagulans* RK-02 could affect intestinal inflammation by regulating cytokines, inhibiting active oxygen, and enhancing phagocytosis.²⁵ A clinical investigation showed that consumption of *B. coagulans* GBI-30, 6086 increased the level of tumor necrosis factor- α in response to adenovirus exposure or influenza A exposure after 30 days of treatment.²⁵

Additionally, *Bacillus coagulans* have been shown to modulate the immune system by production of short-chain fatty acids such as butyric acid and stimulating the production of IL-10.¹⁹ Following activation of host immune cells, the consumption of *B. coagulans* can also strengthen the host immune system and relieve inflammation through cell-derived mediators.²⁴ *B. coagulans* modify the production of immune and growth factors, anti-inflammatory cytokines, and chemokines.²³ Certain strains of *B. coagulans* can act as an adjunct in the management of inflammatory diseases, with a basic mechanism of action which is considered to be by the way of Th1\Th2 cell-mediated immune responses.²⁵ For example, in some cases, the consumption of *B. coagulans* can significantly down-regulate inflammatory immune factors, such as interferon-gamma (IFN γ), interleukin (IL), and tumor necrosis factor (TNF), without altering normal regulatory cytokines.²⁵ Similar to the increase in pro-inflammatory cytokines and immune-activating factors, there is a strong increase in anti-inflammatory cytokines levels also by some of the strains of *B. coagulans*.²⁵ Research studies have evaluated the ability of probiotics to influence host cells via specific bacterial cell wall components, and interactions of Toll-like receptors (TLRs) with secreted metabolites, through influencing innate immune defense mechanisms.²⁵

2.3.3. Regulation of metabolism

B. coagulans GBI-30, 6086 has been shown to help digest plant proteins, such as peas, soybeans, and rice, reduce the number of proteins transported to the colon, and reduce the possibility of proteins being fermented into toxic metabolites by intestinal microbiota.²⁶ Therefore, *B. coagulans* GBI-30, 6086 has dual benefits: enhancing the amino acid bioavailability of plant proteins in the upper intestinal tract and making the microenvironment healthier in the colon.²⁶ Moreover, consumption of *B. coagulans* GBI-30, 6086 with protein can improve protein absorption and utilization.²⁷ *B. coagulans* RCS3 has high levels of β -galactosidase activity and lactate dehydrogenase activity *in vitro*, so it can enhance the lactose digestibility of the lactose intolerant population.²⁷ *B. coagulans* have been shown to promote nutritional metabolism, maintain intestinal integrity, and reduce oxidative stress and diarrhea in piglets.²⁸ Supplementation of *B. coagulans* in the feed also promoted the growth of broilers.²⁹ In cholic-acid-fed rats, soya pulp significantly increased the production of secondary bile acids, such as deoxycholic acid and ω -muricholic acids, which may promote cancer risk in the liver

and colon.³⁰ However, the combination of *B. coagulans* lilac-01 and soya pulp successfully suppressed the increased production of secondary bile acid compared with soya pulp alone.³⁰

2.4. Safety and toxicity

The probiotic *B. coagulans* has no effect of mutagenicity, teratogenicity, or genotoxicity, which has been demonstrated by toxicological safety assessments including *in vitro* bacterial reverse mutation assay, *in vitro* chromosomal aberration assay, micronucleus assay in mice, acute and 90-day subchronic oral toxicity studies in Wistar CrI:(WI) BR rats, and acute eye and skin irritation studies in rabbits.³¹ The No Observed-Adverse-Effect-Level (NOAEL) of *B. coagulans* determined by the acute and 90-day sub-chronic oral toxicity studies in rats is greater than 1000 mg/kg per day, which means 3173 to 95,200 times the recommended daily dose for a 70 kg human.³¹ Safety of long-term consumption of *B. coagulans* GBI-30, 6086 was evaluated with a one-year chronic oral toxicology experiment. No evidence of toxicity was observed in the tested rats even at the highest dose.²⁷ The calculated NOAEL is 1948 mg/kg, which means that chronic consumption of *B. coagulans* GBI-30, 6086 in doses up to 9.38×10^{10} cfu per day is safe.²⁷ Furthermore, no sign of toxicity in the parental generation (male or female) and the F1 offspring was observed in the reproduction toxicity study.³¹ Except for two antibiotic resistance genes that were not easy to transfer, no other genes with potential safety risks were retrieved in the genome of *B. coagulans* GBI-30,6086.³² Another investigation demonstrated that a commercial strain of *B. coagulans* *Unique IS2* had high genotypic and phenotypic stability and the strain had no mutation, no cytotoxicity, and no enterotoxin gene.⁸ Probiotics are considered to be safe with their long history usage.³² But, consumption of probiotics in large quantities in immune-compromised patients may create safety issues.³²

2.5. Application in dentistry

From the promising results of the studies using *Bacillus coagulans* probiotic in medical condition like gastrointestinal disorders, vaginitis, rheumatoid arthritis, toxicity of heavy metals, sport, and hyperlipidemia, recently researches are being focused on this probiotic and its effects on oral diseases and conditions. Furthermore, recent studies have shown that, these probiotics have a therapeutic benefit in dental caries prevention by decreasing the number of cariogenic bacteria, such as *Streptococcus mutans*.⁸ Probiotics may function through various mechanisms, including the production of antimicrobial metabolites, immunomodulation, mucosal barrier enhancement, and microbial flora shift through competition for cell adhesion with pathogenic strains.³³ The application of probiotics for periodontal disease management is an active research field. There have been conflicting results based on several individual studies assessing the effects of probiotics on gingival inflammation and on periodontal diseases. For instance, Ikram et al. showed no improvement in PI and GI in patients with gingivitis after probiotic use, while other reviews concluded that probiotics could improve PI and GI.³⁴ A previous systematic review was unable to assess the immunological benefits of probiotic supplementation due to limited studies; however, the included individual studies indicated an immunomodulatory effect of probiotics.³⁴ Microbiological findings suggested that probiotic supplementation reduced periodontopathogens in subgingival plaque samples; however, there is conflicting evidence in the literature.³⁴

2.5.1. Dental caries

A study was conducted in 2011 to evaluate the effect of probiotics on salivary *Streptococcus mutans* counts in Indian children. A total of 150 healthy children (7–14 years) received placebo powder (n = 50), a freeze-dried powdered combination of *Lactobacillus rhamnosus* and *Bifidobacterium* species (n = 50), or a freeze-dried powdered

preparation of *B. Coagulans* (n = 50) for 14 days. In both probiotic groups, the culture counts of *S. mutans* in saliva decreased significantly ($P < 0.001$), suggesting that *B. coagulans* is a low-cost probiotic for preventing and treating dental caries in children.³⁵

A clinical trial was conducted in 2020 in India to evaluate the Effect of Probiotic *Bacillus coagulans* Unique IS2 on Mutans Streptococci and Lactobacilli Levels in Saliva and Plaque in children.⁸ In this double-blind, randomized, placebo-controlled study, 48 children with ages ranging from 5 to 15 years were divided into two groups, the probiotic and placebo groups. Chewable tablets with and without probiotic *Bacillus coagulans* Unique IS2 were administered for two weeks. Stimulated saliva samples and plaque were collected at baseline and at the end of 14 days to measure the pH, mutans streptococci, and lactobacilli count of saliva and plaque using chairside kits. Results showed a statistically significant reduction in mutans streptococci and lactobacilli counts of both saliva and plaque samples observed in the *B. coagulans* Unique IS2 treated group after 14 days of administration compared to the baseline and placebo group. They concluded that the probiotic *Bacillus coagulans* Unique IS2 (2 billion cfu) chewable tablet is effective in the reduction and inhibition of caries causing mutans streptococci and lactobacilli levels in saliva and plaque in children.⁸

2.5.2. Periodontal diseases

A double-blind, placebo-controlled, prospective pilot study was done to evaluate the clinical efficacy and microbial impact of probiotics containing *Bacillus coagulans* (100 CFU/tablet) in the treatment of moderate to severe plaque-induced gingivitis. Thirty subjects with plaque-induced were enrolled in the study. Gingival Index (GI) and Plaque Index (PI) were assessed at baseline along with saliva sample collection for glutathione peroxidase (GPx) activity analysis and to determine the load of lactobacilli. Participants were randomly provided with chewable tablets to be consumed 3 times daily for 3 months containing 100 million colony forming units (CFU)/tablet of *B. coagulans* or placebo tablets. Assessment of GI, PI, and saliva sampling was repeated after 3 months. Results showed that mean GI and mean PI did not differ significantly between both groups at baseline, but at re-evaluation, mean GI, and bleeding on probing of the probiotic group were both significantly lower than in the placebo group. In the probiotic group, mean glutathione peroxidase activity (Gpx) was significantly lower than in the placebo group at re-evaluation. Hence the consumption of probiotics containing *Bacillus coagulans* seems to modulate inflammatory response in plaque-induced gingivitis.³⁶

To the best of our knowledge, there are no studies where the effects of these probiotics on microbiological and immunological parameters in periodontitis have been assessed. Hence more studies to be initiated for a better understanding of the effectiveness of probiotics containing *Bacillus coagulans* on periodontal variables.

3. Current perspectives and challenges

Even though different mechanisms of action had been revealed in some studies, the exact molecular mechanisms, especially the probiotic effector molecules of *B. coagulans* strains are poorly known till now.³¹ It is anticipated that, through the accumulation of genomic data of *B. coagulans*, future genetic studies may explain the exact molecular mechanisms of beneficial action of *B. coagulans* and these researches will enable a clear perception of probiotic gene-functional relationships.³¹

Until now, the effectiveness of *B. coagulans* in the management of human gastrointestinal diseases and other medical conditions has been illustrated in many clinical trials.^{20–21} Pertaining to toxicology experiments and the historical data of long-term usage of *B. coagulans* have also explained its excellent safety.²⁸ Considering the high stability of *B. coagulans* in production, storage, transportation, and administration due to its spore-forming capability, *B. coagulans* will undoubtedly play a more major role in the probiotic treatment of human oral diseases in the

future.³⁷

Probiotics enjoy the GRAS status and are freely consumed worldwide without any safety concerns. Probiotic efficacy and safety have been revealed in different animal and human clinical trials. But some research studies have raised issues regarding their safety and dose in immune-compromised individuals.³⁷ Although *Bacillus* probiotics have an overall excellent health-promoting record, especially in preventing and curing different medical, their uses in dentistry are still under investigation.³⁸ Their usage in the patient population particularly for the terminally ill, pediatric, and geriatric population should be assessed and synchronized properly as reports related to bacteremia in an immune-compromised patient treated with spore former and other probiotics have been recorded.³⁹ However, the importance of identification to strain level is also important to detect and eliminate any causal link between probiotics and strains isolated from immune-compromised hosts. So, it is crucial to acknowledge that clinical trials of these products should include people with low immunity in their target samples.

4. Conclusion

Because of its probiotic efficacy and discrete gastric life cycle, *B. coagulans* has shown superior potential in the management of various conditions in humans. By direct regulation or indirect modulation of the host-microbial ecosystem, *B. coagulans* plays an astounding role in obliterating infections and attenuating diseases in majority of the human tissues.

Besides, the ability of *B. coagulans* to maintain host-microbiota homeostasis can also aid in the prevention of oral diseases and the promotion of oral health. Hence the favorable effects of *B. coagulans* result from collective and interdependent processes, necessitating the host microbiota, immune system, general metabolism, etc. More research studies are required in the field of dentistry with *B. coagulans* to understand its molecular mechanisms in oral diseases.

Yet, there are numerous *B. coagulans* strains with different origins, the probiotic properties of which are strain-dependent. Hence in the future, it may be beneficial to integrate various strains of *B. coagulans* to augment their effects on oral diseases.

Ethics statements

The review did not include any human subjects or animal experiments.

Declaration of competing interest

Authors declare that they do not have a conflict of interest in any capacity including competing or financial.

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Contributors

Aysha Jebin contributed to literature search and writing the manuscript. Aparna Suresh reviewed and revised the manuscript. Aysha Jebin prepared the figures and tables and Aparna Suresh guided and advised the topic of this article.

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