



Potential Of Probiotics and Natural Ingredients As Antibiofilm And Antibacterial : A Systematic Review

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Abstracts. Biofilms are surface-adhering communities of microorganisms that produce extracellular polymeric substances (EPS) and can grow on any surface, including metal, plastic, glass, soil particles, stainless steel, wood, and biotic surface. biofilm infections lead to different disorders, for instance, diabetes mellitus, dental caries, medical implants and wound infections that significantly affect the quality of life, cancer development, and subsequently, increase the global morbidity rate. This study aims to summarize the recent evidence supporting the potential of probiotic and natural ingredient as antibiofilm and antibacterial using a PRISMA-oriented (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement. This review found significant aspects exemplified by the properties of probiotics and natural ingredients related to as antibiofilm and antibacterial for further indepth studies to make it into pilot scales.

Keywords : probiotic, natural ingredients, biofilm, antibacterial.

1. INTRODUCTION

Biofilms are sessile microbial communities that form on biotic and abiotic surfaces through the secretion of extracellular polymeric substances that enhance adherence to the surfaces and microbial aggregation(1). Biofilm is an intricate microbial community. Proteins, lipids, glycopeptides, hydrated polysaccharides, and extracellular DNA make up its structure. It further consists of some organism species, such as fungi, viruses, and bacteria, rooted in an extra cellular matrix (2). According to the National Institutes of Health (NIH), biofilms are involved in approximately 65% and 80% of all microbial and chronic infections, respectively. In the clinic, microbial biofilms through colonization on implants (prosthetic heart valves, catheters and joint replacement) and medical devices, account for hospital-acquired infections that make the patients easily infected by certain pathogens(3). Biofilms are surface-adhering communities of microorganisms that produce extracellular polymeric substances (EPS) and can grow on any surface, including metal, plastic, glass, soil particles, stainless steel, wood, and biotic surface (4). When the term biofilm is mentioned, it is usually associated with relevant risks responsible for human diseases, antibiotic resistance, infections, and difficulty controlling by being resistant to disinfection and cleaning processes (5) These complications are primarily caused by harmful, detrimental microorganisms such as *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica*, and *Candida albicans* (6) Biofilm formation is a dynamic action whereby

bacteria attach readily and secrete EPS when they contact a surface. Several factors may alter the attachment of the bacterial cell to biotic and abiotic surfaces. These factors include the mobility of bacteria using (flagella, pili, fimbriae and other motile structures), properties of surfaces (roughness, surface hydrophobicity, forces), signalling molecules and environmental conditions (nutrients availability, pH, temperature, flow velocity) (7,8).

Schematically, the formation of a differentiated biofilm requires five maturation stages: (i) initial attachment of planktonic bacteria (reversible) to a surface; (ii) production and secretion of EPS and or other means of docking, and specific adhesins (flagella, autotransporter proteins, fimbriae, curli fibers, and F-type conjugative pilus) that drive the transitional attachment from reversible to irreversible, (iii) early-maturing of biofilm architecture as a super cellular structure; (iv) late-maturing of microcolonies and evolution into a mature biofilm; and (v) detachment of cells from the biofilm and dispersion into the surrounding environment(9)

Moreover, biofilm infections lead to different disorders, for instance, diabetes mellitus, dental caries, medical implants and wound infections that significantly affect the quality of life, cancer development, and subsequently, increase the global morbidity rate (10) Hardly are biofilms detectable with routine diagnostic tests; therefore, the management of their infections are challenging in the clinic, Methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus mutans*, *Pseudomonas aeruginosa*, *S. epidermidis* and *Gardnerella vaginalis* are the most common biofilm formers in the clinic (11) The biofilm acts as a protective barrier and provides resistance against antibiotics, degrading enzymes, protozoan grazers and host immune response. Different strategies like new generations of antibiotics and the inhibition of biofilm formation by quorum sensing (QS) inhibitors have been developed. Due to the challenges of these therapeutic agents in the clinic, there is a demand for developing new strategies. Recent evidence indicates that one of the strongest options for fighting pathogenic biofilms would be probiotics. A certain type of LAB biofilm could be used as a protective biofilm against pathogens and their associated biofilms.

Probiotics are living bacteria that confer a health-related profit to the host when administered in acceptable doses. This action of probiotics is mediated by interacting with host gut microbiota. Probiotics adhered to the intestinal epithelial tissue enhance epithelial barrier function, which is essential to the host defense system in preventing infection and infammation from pathogens (12) The major effects of probiotics involve improved adhesion to intestinal cells, inhibition of pathogen adhesion, production of antimicrobial compounds, and modulation of the immune system. Moreover, some probiotics inhibit biofilm formation by pathogens (13) Therefore, the capability of probiotics to colonize the gastrointestinal (GI) tract is important to

prevent the adhesion and growth of pathogens that can cause infection (14) Lactobacillus species, Bifdobacterium species, Escherichia coli, and Streptococcus species commonly enhance the host immune system in actions that occur either individually or in combination. Lactic acid bacteria produce secondary metabolites with antimicrobial activity, such as hydrogen peroxide, acids, and bacteriocins (15). They also synthesize biosurfactants that interfere with the adhesion and biofilm formation by pathogens on medical devices. High throughput approaches including transcriptomics, metabolomics, proteomics and metagenomics have revealed that probiotics present beneficial for the host and they can modify host mucosal and systemic immune responses and protect the host against pathogens. Hence, the development of antibiofilm strategies is therefore a major interest and currently constitutes an important field of investigation in which environmentally friendly antibiofilm molecules or organisms are highly valuable. The same effect will work on antibiotics and make antibiotic therapy only kill strains without biofilm. It is noteworthy that drug residues in human, multiple resistance, allergy, and gastrointestinal bleeding and other problems would arise after long-term application of common antibiotics (16)

Traditionally, humans have utilized crude extracts of medicinal plants as curative agents for various ailments. Plant extracts and other biologically active compounds isolated from leaves, stems, and roots have gained interest in anti-biofilm activity. However, medicinal plants are mostly used to treat bacterial infections due to their bioactive secondary metabolites. Natural products derived from medicinal plants have proven to be an abundant source of biologically active compounds, and many of them have been the basis for the development of new lead chemicals for pharmaceuticals (17). This study of (18) also suggests that *S. grandiflora* extract possesses compounds with potential antimicrobial properties and aqueous extract of *S. grandiflora* leaf showed evidence of high anti-biofilm and anti-bacterial activity property against *S. aureus*. (19) have reported the use of *Camellia oleifera* seed dreg extract and its application has the potential to be developed as an alternative agent to control microbial biofilm formation, or can be used as an adjuvant compound for infectious disease control. Therefore, we focused on the possibility of using these probiotics, natural ingredients as prophylaxis or therapeutic agents against pathogenic biofilms and antibacterial, and the development and utilization of natural products with antibacterial and antibiofilm properties is particularly urgent.

2. MATERIALS AND METHODS

Search strategy

International databanks, including Sciencedirect, Pubmed, Google Scholar. Were searched from 10 Years. In the present study, were used to determine synonyms by the following keywords (Probiotic, Antibiofilm, Antibacterial, Natural Ingredients). The inclusion criteria were articles published in English, publication date between 2015 and 2024, and article type (original articles or review articles). The selected articles were identified for analysis.

The first screening to identify potentially relevant studies was based on the title and abstract of the selected articles. Afterward, full-text versions of the screened papers were obtained when available and assessed for inclusion according to the pre-established eligibility criteria. All studies were reviewed by one reviewer and any technical uncertainties were resolved by discussion with a second reviewer by online.

Study eligibility

One reviewer independently screened the titles and abstracts of all records identified during the search. Subsequently, studies were selected based on predetermined inclusion and exclusion criteria. Peer-reviewed full-text articles meeting the following inclusion criteria were considered: (1) studies where probiotic cells are used as main agents to counteract pathogens biofilm formation; (2) the inhibition strategies include displacement, exclusion and competition. The exclusion criteria were: (1) studies focused on the antimicrobial effect of probiotic and natural ingredients cells without performing biofilm assays and quantifying the effects on biofilm culturability, viability, biomass, thickness or other property; (2) studies where biotic surfaces, such as epithelial tissues, are used as contact surfaces for biofilm formation; (3) studies where substances isolated from probiotics metabolism are used; (4) non-original articles (including reviews or reports); and (5) unavailability of the full-text version.

Research Instruments

Access to databases and Microsoft Excel as software for data extraction and analysis were available. The authors independently screened, manually assessed the risk of bias, extracted, and analysed the selected studies according to the eligibility criteria. Any disagreements among authors were resolved through discussion.

Data Extraction and Analysis

The collected data from the selected studies were extracted in the form of tabulation, which consisted of: (1) study authors and the year of publication, (2) title, (3) study subjects, (4) conclusion. Bibliographic details of the studies, such as first author and year of

publication were also retrieved. The extracted data were presented in the form of tables using Microsoft Excel and then manually analysed.

3. RESULT

After the inclusion and exclusion criteria were applied to the search methods, there were (n=1.438) identified studies retrieved from the electronic databases. Based on the screening of titles and abstracts, there were (n=150) studies which were included to be assessed further for full-text eligibility. As a result, there were a total of (n=12) studies included in this review to answer Potential of Probiotics and Natural Ingredients As Antibiofilm and Antibacterial (Figure 1). All extracted data are summarised in Table 1. There was no disagreement in analysing the data and discussions regarding the arrangement of the data extraction writing and the categorisation of the level of evidence of each research conducted between the authors through online and offline meetings.

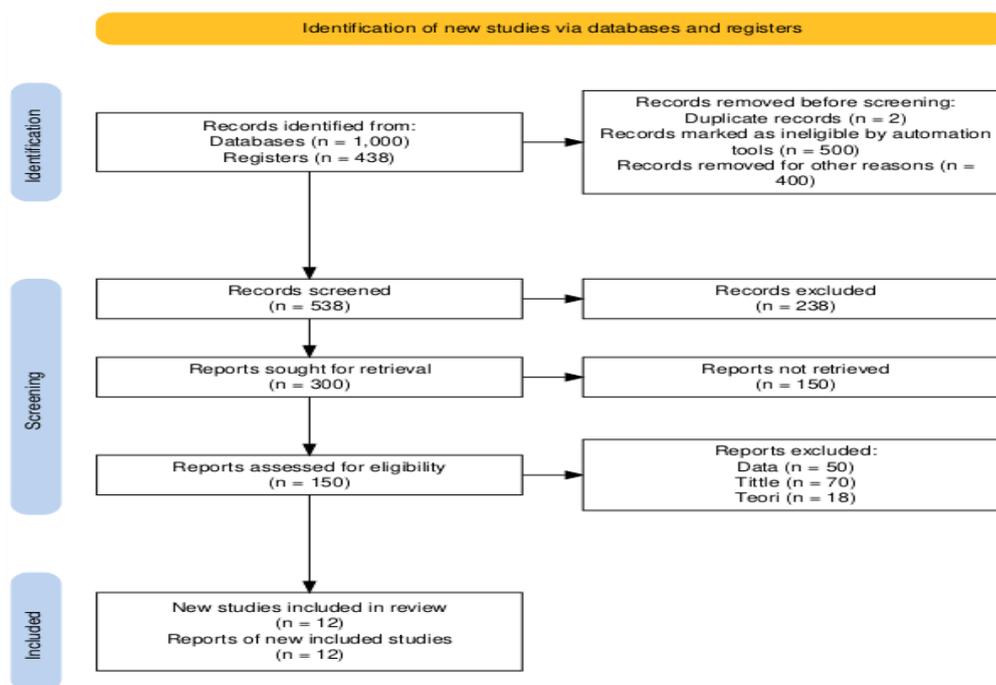


Figure 1. Overview Prisma Diagram Systematic Search Results Using Preferred Reporting Items For Systematic Reviews

Potential of Probiotic and natural Ingredients as Antibiofilm and Antibacterial

Investigated of that used probiotics as antibiofilm and antibacterial. In general, a reported the two studied *E. coli* isolates showed a satisfactory ability to form biofilms while *E. coli* WW1 is a strong biofilm former as compared to IC2 strain. Interestingly, all probiotics resulted in inhibition of biofilm formation to a similar extent. *B. longum* caused the highest inhibition

(57.94%) in case of *E. coli* IC2 while *L. plantarum* was responsible for 64.57% reduction of *E. coli* WW1 biofilms. *E. coli* WW1 biofilms were negatively influenced by CFMSM of probiotics as compared to IC2 isolate. The multidrug resistant *E. coli* isolates showed sensitivity to CFMSM of all probiotics. In general, the composition of the biofilm changes depending on the age of the biofilm, the LAB strain involved, and environmental conditions such as oxygen, temperature, pH, nutrient availability, and desiccation (20). Moreover, fifteen strains of probiotics belonging to many genera among which *Lactobacillus* and *Bifidobacterium* had antibacterial properties against gram negative and gram positive bacteria (21). In the same cell, free supernatants of probiotics were used and the evidence of antibacterial properties was due to produced organic acids lowering the pH. In addition, bioactive compounds released by probiotics such as bacteriocins and hydrogen peroxide were responsible for their antimicrobial and antibiofilm properties (22).

Several studies have shown that probiotics and natural ingredients have antibiofilm and antibacterial properties such as (23). This study showed that a synbiotic combination of *Lactobacillus rhamnosus* and *Pediococcus acidilactici* with inulin-type fructans displayed growth and biofilm inhibition against *Candida albicans*. (24) have shown that probiotics *L. casei* DSM 20011 and *L. reuteri* DSM 20016 exhibit antimicrobial, anti-adherence, and antibiofilm activities against MDR *P. mirabilis*. Ganthi et al. shown antibiofilm and antibacterial efficacy of extract *S. grandiflora* plays a vital role over biofilm producing pathogens and act as a good source for controlling the microbial population. (18).

Tabel 1. Studies included in the systematic review

No	Study author and years Refrensi	Title	Study objects	Conclusion
1	(25)	Cell free preparations of probiotics exerted antibacterial and antibiofilm activities against multidrug resistant <i>E. Coli</i>	Pathogenic <i>Escherichia coli</i> is causative of multiple clinical syndromes such as diarrheal diseases, meningitis and urinary tract infections. In this work, we to control multidrug-resistant <i>E. coli</i> and reduce their ability to form biofilms evaluated the efficacy of probiotics.	In conclusion, the antibacterial effects of cell-free preparations obtained from probiotic against multidrug-resistant <i>E. coli</i> support their effective use as antimicrobial alternatives and widen their applications in medicine and food bio-preservation as well as the possibility to eradicate biofilms formed by pathogenic <i>E. coli</i> .
2	(26)	Biosurfactant derived from probiotic <i>Lactobacillus acidophilus</i> exhibits broad-spectrum antibiofilm activity and inhibits the quorum sensing-regulated virulence	A biosurfactant derived from the probiotic strain <i>Lactobacillus acidophilus</i> was tested against three Gram-negative bacteria to evaluate its inhibitory potential on their biofilms, and whether it affected the virulence factors controlled by quorum sensing (QS)	The extracted biosurfactant showed an antibacterial, antibiofilm, and anti-QS activity against different Gram-negative bacterial pathogens. In vitro studies have shown that the extracted biosurfactant inhibited the formation in the tested bacterial strains by its ability to decrease the swarming motility and its ability to regulate the

No	Study author and years Refrensi	Title	Study objects	Conclusion
				virulence factors, such as pyocyanin, elastase, and protease.
3	(27)	Anti-bacterial and antibiofilm activity of probiotic bacteria against oral pathogens	In this study, three lactic acid bacteria (LAB), isolated from barley, traditional dried meat and fermented olive were characterized and tested for their anti-bacterial and antibiofilm activities against oral	The tested LAB fulfilled several criteria to be used as a probiotic microorganisms, including resistance to gastrointestinal tract, adherence to hydrocarbons, auto and co-aggregation activity as well as susceptibility to some antibiotics. Moreover, those strains inhibited planctonic bacteria growth and biofilm formation.
4	(28)	A novel probiotic strain of <i>Lactobacillus fermentum</i> TIU19 isolated from Haria beer showing both in vitro antibacterial and antibiofilm properties upon two multi resistant uropathogen strains	Probiotic properties, such as survival in simulated gastrointestinal fluid, antioxidant activity, β -galactosidase producing ability, high cell surface hydrophobicity, adhesion ability to epithelial cells, and strong biofilm producer. The growth inhibitory and antibiofilm activities were shown against two uropathogens. All these results suggest that <i>L. fermentum</i> TIU19 can be explored as a potential probiotic with antagonistic activity against MDR uro-pathogenic <i>E. coli</i> and <i>E. faecalis</i> .	<i>L. fermentum</i> TIU19 has safety properties in vitro and inhibitory activity upon multi resistant uropathogens <i>E. coli</i> and <i>E. faecium</i> . Thus, this strain harbor promising probiotic traits, but further analyses are needed to verify in vivo the probiotic behavior of <i>L. fermentum</i> TIU19.
5	(29)	Antimicrobial and Anti-Biofilm Activity of Polymyxin E Alone and in Combination with Probiotic Strains of <i>Bacillus subtilis</i> KATMIRA1933 and <i>Bacillus amyloliquefaciens</i> B-1895 against.	Investigates the antibacterial and anti-biofilm activity of polymyxin E alone and in combination with the cell-free supernatants (CFS) of the tested probiotic bacilli, <i>Bacillus subtilis</i> KATMIRA1933 and <i>Bacillus amyloliquefaciens</i> B-1895 against the selected <i>Acinetobacter</i> spp. starins. Three isolates of <i>Acinetobacter</i> spp., designated as <i>Acinetobacter</i> spp. isolate 1; <i>Acinetobacter</i> spp. isolate 2, and <i>Acinetobacter</i> spp.	The antimicrobial and anti-biofilm activities of polymyxin E were improved and showed synergism when combined with the CFS of the tested probiotic bacilli against planktonic and biofilm-associated cells of the selected <i>Acinetobacter</i> spp. Isolates
6	(30)	Antibacterial and anti-biofilm activities of probiotic <i>Lactobacillus plantarum</i> against <i>Listeria monocytogenes</i> isolated from milk, chicken and pregnant women.	The antibacterial and anti-biofilm activity of <i>Lactobacillus plantarum</i> ATCC 14917 (<i>L. plantarum</i>) against <i>L. monocytogenes</i> isolates was investigated. A cross-sectional study was conducted from August 2021 to January 2022 to collect 300 samples of pasteurized milk, chicken fillets, and stool from pregnant women admitted to	<i>L. plantarum</i> exhibited potential antibacterial and anti-biofilm effects against <i>L. monocytogenes</i> isolates, further research is necessary to explore its full probiotic potential. Lastly, it is crucial to monitor the prevalence and antimicrobial resistance profile of <i>L. monocytogenes</i> in dairy and meat products to enhance their safety.

No	Study author and years Refrensi	Title	Study objects	Conclusion
			outpatient clinics of hospitals.	
7	(18)	In vitro anti- biofilm and anti-bacterial activity of Sesbania grandiflora extract against Staphylococcus aureus	Quantification of Extracellular polymeric substance (EPS) particularly protein and carbohydrate were calculated.	The antibacterial activity of S. grandiflora extract against the bacterial strain S. aureus showed that the extract were more active against the strain. Anti-biofilm and antibacterial efficacy of S. grandiflora plays a vital role over biofilm producing pathogens and act as a good source for controlling the microbial population.
8	(31)	Antimicrobial and anti-biofilm effects of probiotic Lactobacillus plantarum KU200656 isolated from kimchi.	KU200656 showed high tolerance to artificial gastric acid (99.48%) and bile salts (102.40%) and this strain was safe according to antibiotic sensitivity test.KU200656 coaggregated with pathogenic bacteria and exhibited antibacterial activity and anti-adhesion properties against pathogens. The cell-free supernatant (CFS) of KU200656 inhibited biofilm formation by pathogenic bacteria.	Production of antimicrobial agents, and inhibition of pathogen adherence due to the high adhesion ability of KU200656. the CFS of KU200656 exhibited an anti-biofilm effect at 1/2 MIC and had an ability to regulate the transcription level of biofilm-associated genes like the virulence regulatory gene, flagellar motility gene, and intracellular adhesion gene.
9	(2)	The antimicrobial and antibiofilm effects of three herbal extracts on Streptococcus mutans compared with Chlorhexidine 0.2% (in vitro study)	Production of antimicrobial agents, and inhibition of pathogen adherence due to the high adhesion ability of KU200656. the CFS of KU200656 exhibited an anti-biofilm effect at 1/2 MIC and had an ability to regulate the transcription level of biofilm-associated genes like the virulence regulatory gene, flagellar motility gene, and intracellular adhesion gene.	The extracts of the three plants possess antibacterial and antibiofilm activities against S. mutans, with Carum copticum and Phlomis bruguieri exhibiting the highest and lowest activities, respectively. The antibiofilm activity of the three extracts was lower than the common 0.2% Chlorhexidine mouthwash. Since medicinal plants are abundant in Iran and pose fewer side effects than chemicals, research to identify candidate plants in dental and oral care is essential.
10	(32)	Antimicrobial and antibiofilm activities of pomegranate peel phenolic compounds: Varietal screening through a multivariate approach	Antimicrobial activity of the peel (exocarp and mesocarp) from seven Punica granatum varieties (Wonderful, Mollar de Elche, Primosole, Sassari 1, Sassari 2, Sassari 3, and Arbara Druci) grown in Sardinia (Italy) were evaluated. The antimicrobial and antibiofilm activities of each PPE were further tested in vitro against Staphylococcus aureus , Listeria monocytogenes , Salmonella bongori , Escherichia coli , Lactiseibacillus casei and Limosilac- tobacillus reuteri .	Antimicrobial activity was shown against S. aureus and L. monocytogenes strains, whereas less, even no activity was found against S. bongori and E. coli strains. The PPEs from Mollar de Elche, Primosole, and Sassari 3 showed the highest antimicrobial activities at concentrations that varied from 0.19 to 1.50 mg/mL, with biofilm activity being reduced by more than 70%. These activities were positively related to the punicalagin, flavonoid, and chlorogenic acid content of the extracts.

No	Study author and years Refrensi	Title	Study objects	Conclusion
11	(33)	Antibacterial and antibiofilm activity of Lactobacillus strains secretome and extraction against Escherichia coli isolated from urinary tract infection	The antibacterial and antibiofilm activity of secretome and extraction of both Lactobacillus strains were evaluated against isolated E. coli samples. L.acidophilus and L. casei were able to tolerate pH 3, bile salts, and pancreatic enzymes.	These strains had significant antimicrobial effect against E. coli isolated from patients with UTI. Showed the antibiofilm effect of Lactobacillus strains against E. coli isolates.the antibiofilm effect of Lactobacillus strains against E. coli isolates. The effects of L. acidophilus and L. casei probiotics are not limited only to promote of human healthy, it also provides antibacterial effect against pathogenic bacteria.
12	(34)	Antibacterial activities of Miang extracts Robusta coffee extracts inhibit quorum sensing activity in Chromobacterium violaceum and reduce biofilms against Bacillus cereus and Staphylococcus aureus`	Bacillus cereus and Staphylococcus aureus cause foodborne intoxication in humans and animals. Pathogens can produce biofilms controlled by the quorum sensing system. The study aimed to investigate the antibacterial, antibiofilm, and anti-quorum sensing activities of Coffea canephora P. ex Fr. (Robusta coffee) extracts against B. cereus and S. aureus.	potential therapeutic benefits of Robusta coffee extracts in inhibiting the growth, biofilm, and quorum sensing of both B. cereus and S. aureus. The results put forward an alternative strategy to control the foodborne intoxications caused by both pathogens.

4. DISCUSSION

Interpretation of findings

The present systematic review aimed to investigate the effects of probiotics and natural ingredient as antibiofilm and antibacterial. The findings of this review contribute to knowledge of using probiotics and natural ingredient as antibiofilm and antibacterial. The analysis included randomized, placebo controlled trials. These rigorous study designs provide robust evidence to evaluate the efficacy of probiotics and natural ingredients in this context. Overall, the results suggest that probiotics and natural ingredients the incidence of biofilm formation and antibacterial.

The analysis included a total of 12 studies, providing valuable insights into the potential benefits of probiotic and natural ingredients as antibiofilm and antibacterial (tables 1), within the studied probiotic strains, L. paracasei, L. plantarum, and B. lactis are most commonly studied. Due to the complexity of probiotic live and dead cells, or their byproducts such as SCFA, bacteriocin, and peptidoglycan, the effects on antibiofilm and antibacterial.

Limitations clinical

Several limitations of this systematic review should be acknowledged. Firstly, the included studies varied in terms of study design, probiotic strains used, intervention duration, and outcome measures assessed. This heterogeneity may introduce potential biases and limit the generalizability of the results. Additionally, the sample sizes and numbers of the included clinical studies were relatively small, which could impact the statistical power and precision of the findings. Furthermore, the quality assessment revealed a high risk of bias in one study due to incomplete outcome data, suggesting a need for further improvement in the reporting of study results. Another limitation is the potential for publication bias, as the analysis relied on published studies and such studies as with negative results may have not been published. Lastly, acknowledging the study limitation in the scarcity of papers compared to other systematic reviews.

5. CONCLUSION

In conclusion, this systematic review provide evidence supporting the potential benefits of potential probiotics and natural ingredients as antibiofilm and antibacterial. However, the heterogeneity among the included studies, limited sample sizes, potential publication bias interpreting the results. Future well-designed studies including both clinical and preclinical approaches with larger sample sizes and standardized outcome measures are warranted to further investigate the effects of probiotics and natural ingredients as antibiofilm and antibacterial

CONFLICT OF INTEREST

Authors should made a conflict of interests disclosure statement or a declaration that they do not have any conflicts of interest. Authors should disclose at the time of revision any financial arrangement they may have with a company whose product is pertinent to the submitted manuscript or with a company making a competing product. Such information will be held in confidence while the paper is under review and will not influence the editorial.

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AUTHOR CONTRIBUTION

A paragraph should explain how each author (initially) contributed to the manuscript. The contributions can be stated as the examples given: concepts or ideas, design, the definition of intellectual content, literature search, experimental study, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review, etc. The subjects of each contribution can be stated differently depending on each author.

LIST OF ABBREVIATIONS

MDA: malondialdehyde; DM: diabetes mellitus; NAD: nicotinamide; STZ: streptozotocin; FBG: fasting blood glucose; HE: hematoxylin and eosin; ECM: extracellular matrix; ROS: Reactive oxygen species.

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