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The Role of Probiotics as Gastrointestinal Infections Treatment and Prophylaxis: A Review

Leite GGVR[1*] and Damasceno CAV[2]

[1]Medical student at University of Itaúna, Itaúna, Minas Gerais, Brazil

[2]Chief of the Department of Microbiology and professor at University of Itaúna, Itaúna, Minas Gerais, Brazil

***Corresponding author:**

Gabriel Gomes Vieira Ribeiro Leite, Medical student at University of Itaúna, Itaúna, Minas Gerais, Brazil,
E-mail: medgabrielvieira@gmail.com

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1. Abstract

Probiotics are products which contain microorganisms capable of supporting symbiotic relations with native microbiota of many environments. They are widely used and studied due to their capacity of improving biological systems' overall health. Many hypothesis exist surrounding the mechanisms by which every microbe labelled as probiotic is the cause by which system health is enhanced by its presence. The aim of this review was to compile article's data concerning the role of different combinations of probiotics used to treat and prevent gastrointestinal conditions, such as antibiotic-associated diarrhea, pseudomembranous colitis, Helicobacter pylori infections, oral, pharyngeal and Salmonella infections. In general, other than presenting excellent safety records, several probiotic combination registered in clinical trials could prove themselves capable of significantly preventing those infections and some proved to be capable to also treat them once established. The main challenge among the infections studies seems to be oral cavity infections, probably due to microbiota complexity. Nevertheless, probiotics seem to have good prospect for playing a major preventive and protective role in gastrointestinal infections with further investigation to gather sufficient evidence to base treatment protocols.

2. Introduction

The very definition of probiotics was first produced in 1965 by Lilly and Stillwell [1] as bacteria who could increase other bacteria proliferation within biological systems, since then they have had their definition and usage broadly expanded. Currently updated by Hill et al. in 2014, the meaning of probiotics is now fit to describe microorganisms that can improve the health of a system when ingested in sufficient amount [2].

Therefore, such definition is intended to include their effects on many human systems concerning medical sciences, mainly by impacting the resident microbiota, intestinal epithelium cells, the immune system and cell-mediated response to infection and stress.

The most studied species include Lactobacillus, Bifidobacterium, and Saccharomyces [3], but even prior to the first steps investigating probiotics' potential, bacteria described as probiotic have been empirically added to dietary supplementation and foods due to the potential beneficial effects their action could produce for human health, and naturally clinical trials have been extensively conducted to measure and improve probiotic consumption and selection [4]. Further than that, many studies nowadays have provided evidence to support probiotics' use as treatment and prophylaxis of a large array of infections, such as those produced by Helicobacter pylori, Clostridium difficile on the gastrointestinal tract, Streptococcus mutans on caries and periodontitis, many upper and lower respiratory tract infections, inflammatory bowel disease and diarrhea microbes, as well as other diseases.

Not only typical presentation cases management have shown to be improved by probiotics use, but also multi-drug resistant bacteria infections could potentially be considered for probiotics use, amplifying their relevance since those are universally important public health issues.

The major role probiotics could play, if proven to be effective, is to decrease antibiotic use, which has the catastrophic side-effect of

microbial resistance development, other than being a cause of many gastrointestinal conditions themselves, such as very common cases of Antibiotic-Associated Diarrhea (AAD). Mitigating the burdens of diseases and antibiotic use could improve health care morbidity, mortality and cost worldwide [2].

Further on, the interest on probiotics is also inspired by high safety standards extensively recorded on literature [6,7], even on immunocompromised HIV patients [8] and children [9].

We present this article as an endeavor to produce an updated compilation of current literature concerning probiotic use on several infections and its comparison to traditional antibiotic treatment on terms of prophylactic and treatment effectiveness, safety and outcomes on gastrointestinal infections.

3. Methods

The present review focused research on well-oriented clinical trials concerning probiotic use on AAD, Clostridium Difficile Infection (CDI), Helicobacter pylori infection, Streptococcus mutans oral infections, Streptococcus and Bacilli pharyngeal infections and Salmonella infection.

Article research was conducted on PubMed, Scielo, Science Direct and Medline bases. The following key-words were used: "probiotics", "treatment", “prevention", “Clostridium difficile infection”, “Helicobacter pylori”, “Salmonella”, “oral infection”, “microbiota”, “pharynx infection”, “antibiotic" as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present.

Enters and records identified in the electronic data banks were exported to the platform Rayaan, used in selection. Studies were initially filtered by title and abstract independently and those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis.

Articles of opinion and isolated case reports were the only automatic exclusion criteria for article analysis, and no case complications were considered as to differ among infection presentations. Articles were also not excluded based on language, date or place of conduction.

4. Results

4.1. Probiotics Use on Antibiotic-Associated Diarrhea (AAD)

AAD is a common and undesirable adverse effect of antibiotic treatment and can present itself disregarding previous patient condition. It occurs in as many as 30% of patients [10] and is characterized by disruption of gut microbiota, decreased intestinal Short Chain Fatty Acid (SCFA) concentrations, accumulation of luminal carbohydrates and colonic bile acids, altered water absorption, and ultimately diarrhea [11].

Several articles evaluated probiotic treatment in children, since they are particularly at risk with incidence of AAD being as high as 35% [12], and all conclusive ones suggested probiotics to be effective in preventing and treating AAD, despite previous theoretical conjectures which suggested that probiotic treatment was a logical flaw on AAD [13].

Compiling thirty-three studies with more than 6300 patients ranging from 0 to 18 years-old, organized in random groups for probiotic treatment, placebo and no treatment at all it was recorded precise benefit for probiotics. Diarrhea incidence after 5 days to 12 weeks of follow-up were shown to be 8% in the probiotic group, in comparison to 19% in the control group (risk ratio RR 0.45, 95% confidence interval CI 0.36 to 0.56; I^2 = 57%, 6352 participants; 95% CI 7 to 13). Low dose studies (< 5 billion CFUs per day) showed that the incidence of AAD in the probiotic group was 8% compared to 23% in the control group (4038 participants; RR 0.37; 95% CI 0.30 to 0.46; P = 0.06) and high dose studies (≥ 5 billion CFUs per day) recorded incidence rates of 13% in the probiotic group compared to 23% in control group (4425 participants; RR 0.54; 95% CI 0.42 to 0.70; P <0.00001; I^2 = 68%) [14]. The results suggested the effectiveness of treatment to be dose-dependent.

Comparing safety among 24 of those trials (4415 participants) which reported on adverse events, none reported serious adverse events attributable to probiotics.

Although also insensitive due to numerous subgroups consideration, another compilation of 82 randomized trials showed statistically significant AAD reduction results by associating probiotics to antibiotic treatment (relative risk, 0.58; 95% CI, 0.50 to 0.68; P < .001; I(2), 54%) [15].

On the strands used, Lactobacillus rhamnosus GG (LGG) had the better record of effectiveness and tolerability on prevention of AAD, and even though Clostridium difficile is broadly known to cause around 20% of AAD as an opportunistic pathogen [16], it is better analyzed independently since a 2018 article reported that Lactobacillus casei was considered as presenting better efficacy and moderately better tolerance for its infections [16]. Another strong recommendation strand is claimed to be Saccharomyces boulardii, although evidence is still lacking and current results are still behind LGG [18].

A double-blind randomized study conducted in Australia also confirmed LGG effectiveness combined with Bifidobacterium lactis (Bb-12) and Lactobacillus acidophilus (La-5). Children were given 200g/day probiotic yogurt versus pasteurized yogurt as placebo, with narrower population consisting of 72 children of which 70 completed treatment, no severe diarrhea (stool consistency ≥6, ≥3 stools/day for ≥2 consecutive days) episodes were reported in probiotic group while six presented in placebo, and only one minor diarrhea (stool consistency ≥5, ≥2 stools/day for ≥2 days) episode was presented in probiotic group compared to [21] in placebo [19].

4.2. Probiotics Use in Clostridium Difficile Infection (CDI)

The usual Clostridium difficile infection causes pseudomembranous colitis and it is also the leading opportunistic pathogen to cause AAD. Disruption of gastrointestinal microbiota is the most evidence-based infection etiology, since normal conditions usually suffice for

preventing Clostridium infection [20].

A recent consensus guidelines published by the British Society of Gastroenterology did mention probiotics as relatively effective treatment to CDI, although it suggested that its use should be restricted to very uncommon scenarios and never as first line treatment or prophylaxis, opposing antibiotics, claiming evidence was lacking [21]. Nevertheless, several articles were then conducted, including a Cochrane database article, indicating that guidelines should be revised, since probiotics have the highest quality evidence among cited prophylactic therapies [22].

In order to base this claim, the study compiled thirty-nine studies, concluding that probiotic prophylaxis should reduce the risk of C. difficile-associated diarrhea by 60%. Incidence of presentations were 1.5% in probiotic group and 4.0% in control (RR 0.40, 95% CI 0.30 to 0.52), which was considered to be statistically significant, even though it noted the heterogeneity of results when pooled.

Even prior to the guideline's publication, many articles suggested reasonable evidence that probiotics could indeed prevent CDI in many cases. New mechanisms were even discovered, suggesting probiotics health promotion worked not only through microbiome protection, but also by directly inhibiting pathogen growth, neutralizing toxins and modulating inflammatory response [23,24].

The most successful treatment seems to be a multi-strand formula, combining L. acidophilus CL1285, L. casei LBC80R, L. rhamnosus CLR2, Bio-K+, which also showed an excellent safety profile, even in preventing C. difficile hospital infections [25].

These recent results should suffice safety evidence that concerned previous researches who found great efficacy outcomes [26-29].

4.3. Probiotics Use in Helicobacter Pylori Infection (HPI)

Helicobacter pylori infections are rather common, affects nearly half the world population and its relevance relies not only on its relation with many gastrointestinal diseases, but also on extragastric manifestations [30]. An alternative to antibiotic treatment is usually described as urgent, mainly due to bacterial resistance development [31]. Thus, the role of probiotics seems to fit perfectly with H. pylori eradication treatment demands.

A recent Chinese study reviewed one hundred and forty results for probiotic eradication therapy in a massive population group (20,215 patients) in order to investigate different probiotics supplementation's effectiveness. All data considered, eradication rates were 84.1% in probiotic group while 70.5% in control, and adverse events rates were 14.4% in probiotic group while 30.1% in control [32].

In general, more than 10 strategies of probiotic treatment were experimented and no statistically significant difference was found amidst the strands. Combined therapy did not show better results or tolerance either. Difference among strands seem to rely on treatment length, being Lactobacillus acidophilus a slightly better choice in in triple therapy of 7 and 14 days, while Saccharomyces boulardii was more applicable for 10-day triple therapy.

Some notable strands properties should also be noted for further investigation, such as L. pentosus LPS16, which lactic acid production has been shown to inhibit both drug-sensitive and drug-resistant H. pylori strains in vitro [33]. The same effect could also be obtained from seven L. bulgaricus strains [34]. The acid-resistant strain L. johnsonii No.1088, isolated from gastric juice of healthy volunteers could suppress H. pylori both in vitro and in a mouse model, and the heat-killed form of the strain also showed antibacterial effects [35,36]. Many hypothesis suggest mechanisms for the antagonism probiotics exert against H. pylori, although molecular studies are still pending for their confirmation [37].

From this review on, few interesting studies were conducted which led to new discoveries and hypothesis concerning probiotics treatment in HPI.

A research conducted on model animals showed significant association of probiotic treatment with reduction on gastric inflammation secondary to HPI, and also suggested that long-term administration of probiotics might have favourable outcomes in H. pylori infection especially by decreasing the risk of development of diseases caused by increased levels of gastric inflammation, such as gastric ulcer [38]. Other than that, the study also confirmed probiotics' colonization reduction capability previously observed.

Clinical researchers have yet failed to report on a probiotic treatment who could alone achieve H. pylori eradication. This is expected to be the great breakthrough of gastric probiotic therapy and it is optimistically indicated to happen as further trials are conducted [37].

4.4. Probiotics Use on Oral Infections

Probiotics are thoroughly studied in oral health problems mainly because periodontal diseases and dental caries are usually treated with systemic use of antimicrobial drugs [39], which can trigger gastrointestinal conditions, as previously exposed, as well as promote bacterial resistance and allergic reactions [40].

Oral microbiota is a delicate subject in the clinics, since the oral cavity is a complex microbiological system that needs homeostasis [41]. In order for microorganisms and toxins to attack oral tissues, they are usually organized in a thin film layer deposited on hard oral tissue (enamel and cementum) called biofilm [42], which is described to be the result of bacterial adhesion, aggregation and co-aggregation to colonize the oral cavity [43].

Although action mechanism for probiotic therapy in oral health is still obscure, they are widely correlated with decreased CFU counts of pathogens [44,45]. A review suggests the very interesting hypothesis of the microbiological dynamic of probiotics in the oral cavity competing for adhesion with pathogens, causing the latter's displacement [46].

A meta-analysis of articles concerning caries development with probiotic therapy recorded a significant decrease in CFU counts of S. mutans after bacteriotherapy, which does not happen with the CFU counts of Lactobacilli. In addition, after treatment with probiotics,

the intervention group had a greater number of patients with low levels of S. mutans CFU counts (< 105 CFU/ml) and fewer patients with high levels (> 106 CFU/ml), which does not occur in the control group [47].

On the other hand, a double-blind clinical trial on 96 children divided on three groups receiving probiotics (B. lactis BB -12), xylitol or sorbitol for control, concluded that early administration of this probiotic strain did not represent its permanent colonization in the oral cavity and that the CFU counts of S. mutans were not significantly affected [48]. In addition, yet another three randomized clinical trials reviewed by Twetman, et al. [49] using L. Rhamnosus and milk as a vehicle for the prevention of dental caries concluded that despite encouraging results and given evidence collected, it is still premature to present probiotics as preventive clinical recommendation, and indicated the need for long-term follow-up in order to establish needed confirmation for the therapy.

Another meta-analysis of 50 clinical trials suggested that probiotic therapy significantly reduces the S. mutans CFU counts (<104 UFC/ml), and that Bifidobacteria are the most significant contributor to this effect, but studies which brought up data to this conclusion has high risk of bias, therefore, forcing researchers to conclude that current clinical evidence is inconsistent in order to make recommendations for the use of probiotics to treat or prevent dental caries [50].

Periodontal conditions and caries, being multifactorial diseases [51], seem to trouble trials with more variables to consider than it is possible to manage to organize data. That is one review's hypothesis to why despite the evidence, it is still impossible to make a statement towards probiotics recommendations in oral health [52].

Many other clinical trials [53,54] were conducted and are currently ingoing investigating other strands in oral health probiotics, such as S. oralis, S. uberis, L. salivarius and S. rattus, other pathogens' CFU counts are being considered as Prevotella intemedia, Agregatibacter actinomycetemcomitans and Porphyromana gingivalis and researchers struggle to extend follow-up time. Nevertheless, the main conclusion seems to remain that probiotics cannot replace daily oral hygiene technique [47].

4.5. Probiotics Use in Pharyngeal Infections

Pharyngeal infections, notably the ones caused by Streptococcus pyogenes, also produces the previously described structure of biofilm. And as well as in the oral cavity, in the pharynx bacteria in biofilms are less sensitive to host defense mechanisms and antimicrobial agents, due to multiple strategies, that involve modulation of gene expression, controlled metabolic rate, intercellular communication, composition, and 3D architecture of the extracellular matrix [55].

In 2012, inspired by the probiotic potential to modulate cavity microbiota to protect it from infections, an in vitro research was conducted to experiment and investigate the functional and immunomodulatory properties of the strains Lactobacillus helveticus MIMLh5 and Streptococcus salivarius ST3 [56], which were highlighted previously by other studies [57,58]. This study concluded that strains MIMLh5 and ST3, alone and in combination, can efficiently adhere to pharyngeal epithelial cells, antagonize S. pyogenes, and modulate host innate immunity by inducing potentially protective effects. In addition, it also reported that their combination resulted in a synergistic effect, according to cytokine induction, that might help the host immune system react to potential pathogens while maintaining a balance between pro- and anti-inflammatory cytokines, thus preventing possible exaggerated responses.

Another in vitro article observed that S. salivarius 24SMB and S. oralis 89a are able to inhibit the biofilm formation capacity of selected pathogens and even to disperse their pre-formed biofilms. Diffusible molecules secreted by the two streptococci and lowered pH of the medium revealed to be implied in the mechanisms of anti-biofilm activity [59].

New strands other than Streptococcus salivarius, probiotic candidates Lactobacillus acidophilus and Lactobacillus plantarum were tested for the same protective properties in a in vitro pharynx cosmos, showing promising results together with many other bacteria native to the natural environment [60]. The article purposes itself to be a preclinical towards future probiotic trials, and no clinical trials were published yet to this review's making date concerning probiotics use in pharyngeal infections that would suffice inclusion criteria, even though given laboratory evidence it poses as a great prospect for a safe upper respiratory infections treatment.

4.6. Probiotics Use in Salmonella spp. Infections

Salmonella spp. Infections are one of the leading causes of acute diarrhea worldwide [61]. As a long known disease, efforts to employ microorganisms therapy, which would today be called probiotic therapy, started even before the first definition of the word itself, in 1959, when Nissle published an article with records of an E. coli strand isolated from a soldier which appeared to be resistant to a diarrhea outbreak and seemed to establish persistent intestine colonization, therefore, suggesting its potential to compete with intestinal infections [62].

Nissle hypothesis' success mechanisms were explained in 2017, when a trial in rats infected with S. enterica serovar Typhimurium showed E. coli strain Nissle 1917 outcompeted the pathogen for iron acquisition [63] which is established as the most important micronutrient for its virulence [64].

Further on, many other probiotics were suggested to alleviate salmonellosis as time progressed. A study identified two non-Saccharomyces species - K. marxianus and Metschnikowia gruessii - as significantly capable of protecting host's intestinal epithelium against disrupting activity from the same Salmonella strain [65].

Animal trials in newly hatched broiler chicken with a multi-species probiotic consisting of Lactobacillus crispatus, Lactobacillus salivarius, Lactobacillus gallinarum, Lactobacillus johnsonii, Enterococcus faecalis and Bacillus amyloliquefaciens showed better and safer re-

sults than traditional antibiotic therapy with oxytetracycline, used as control. Results were significant to the point which probiotic therapy were suggested as preferred choice of treatment66. Other studies with other strands were also published studying probiotics in poultry and rats, many of which were absolutely successful, through different biochemical mechanisms of pathogen inhibition [67-70].

In fact, microbiota seems to play an extraordinarily important role in Salmonella infections, being shown that slight variation in endogenous Enterobacteriaceae could importantly determine host's susceptibility to infection, even in genetically similar organisms [71].

Confirming probiotics effectiveness, several clinical trials in humans replicated in vitro and in vivo animal trials [72]. A randomized controlled trial showed Lactobacillus plantarum 299 could accelerate clearance of non-typhoid Salmonella and reduce infection-related symptoms, which was influenced by gender [73].

Recently, that first E. coli strand isolated by Nissle [62] were subject to bioengineering and successfully inhibited Salmonella colonization via tetrathionate-induced production of microcin H [47]. The strand seems to greatly outcompete Salmonella, using an environmental signal indicative of intestinal inflammation as an inducing molecule, resulting in considerable increase in fitness advantage [74].

5. Conclusion

The quality of evidence for the use of probiotics to treat or prevent gastrointestinal tract infections seems to be uneven. While its usage on AAD, CDI and Salmonella infections have shown reasonably positive clinical results and are already incorporated to protocol therapies, it remains unclear which exact mechanisms, microbiological interactions and method approaches could account for many discrepant results in some trials. The main challenge seems to present in oral infections applications, due to the microbiota dynamics complexity.

In assessing safety, probiotics seems to exceed traditional antibiotic treatment given almost no record of adverse events from all evaluated studies in comparison to the known problematic and often iatrogenic drug therapies. Overall, probiotics seem to have increasingly good prospects in clinical use, even though further research is needed in order to produce evidence for strain selection and effectiveness in specific diseases.

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