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Review Article

LGG^{TM}- A promising therapy in gastro-intestinal infections

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ABSTRACT

Probiotics are live harmless microbes which are a part of normal human gut flora, where they strive to maintain a symbiotic relationship with the human host. To date, thousands of publications exist on their functionality and their impact on prevention and treatment of various diseases. However, one of the most widely studied probiotic strain is *Lactobacillus rhamnosus* GG also known as LGG^{TM}. LGG^{TM} is extensively studied and backed by various health authorities to be effective in various gastro-intestinal tract (GIT) related diseases. Thus, LGG^{TM} based products provide a novel approach for disease prevention and treatment, especially in intestinal inflammatory disorders. It is well recognized that multistrain probiotic products show additional benefits by the virtue of the synergism shown when specific strains are combined. Probiotics strains selected for therapeutic use must retain their characteristics so that they deem to be efficacious for treatment of specific disease. However, in the swiftly emerging global probiotic market, end-users often have a difficult time distinguishing between high quality and poor quality products. This ambiguity impend the effective use of right probiotic strain for the right condition. This review article attempts to alert the end-users to use the right strain that guarantees the beneficial results.

1. Introduction

Probiotics are no sort of invention or discovery; rather it existed in our traditional foods like beverages, yogurt, milk, cheese, salty fishes, since time immemorial.[1] Magnanimous evidence advocates that gut microbiome is very vital and plays a role in epithelial cell proliferation, development and homeostasis of immune system and shielding host's health.[2]

Probiotics have been extensively studied in gastro-intestinal (GI) as well as extra-gastrointestinal conditions. However, there ensues to be incongruence in the data, particularly with respect to extra-gastrointestinal conditions. The strongest evidence in the field of probiotics points to the usage of probiotics in acute diarrhea.[3] 'Probiotic' is a generic term which comprises of species of microbes. Characterizing an individual strain is essential so as to be subjected to a consumer health claim. Several experts agree that the clinical benefits in prevention and treatment of an ailment depend on the specific strain of bacteria and cannot be extrapolated to other strains.[4] Today a sizeable amount of probiotic brands are available in the probiotic market and not all brands of probiotics are equally effective. Considering that, selection of a particular brand of probiotic which would prove to be beneficial in particular condition could be a demanding task.[3]

Among the various probiotics available, LGG^{TM} has become one of the best clinically documented and widely studied probiotic strain. The growing body of evidence suggests its benefits in various diseases especially the ones related to GIT.[5] Doctors are presented with a plethora of LGG^{TM} products due to the concept of generic probiotics. Selecting the right LGG^{TM} strain product that caters benefits in the right condition amidst such a wide array of products is often confusing for the doctors.

This narrative article is an effort to address the contemporary knowledge and landscape of probiotic research revolving around the most interesting strain

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'LGG^{TM}'. The article provides a brief overview on its characteristics, distinguishing parameters and studies carried out in different medical conditions. For the same, a MEDLINE/PubMed search for literature that matches the terms 'probiotics', 'generic probiotics', '*Lactobacillus rhamnosus* GG', 'Clinical trials on LGG', 'Multistrain probiotics' etc. was carried out. Several articles were available relating to each term; however 80 articles among many that instated interest were selected for drafting of this review article.

1.1. Dysbiosis – The single root of all problems

The gut harbours both kinds of bacteria; one is the commensal bacteria which play the role of helpful residents and other is the pathogenic bacteria which play the role of enemies from the within.[6] Under normal healthy condition, the human host and the microbiota within the gut engage in a constant cross-talk and cross-regulation, which creates a homeostatic balance and establishes a symbiotic relationship within the GIT. As a result, the GIT reflects sound health.[7] Overgrowth of harmful opportunistic bacteria is inhibited in a healthy gut.[8]

The gut microbiota and the host engage in a commensal relationship, one where the bacteria flourish in the nutrient rich environment of the gut while the host benefits from the multiple functions provided by the bacteria.[9] The homeostatic balance is extremely important for the well-being of the host. However, in the state of the homeostasis imbalance, microbial alterations take place. Various otherwise subdominant opportunistic bacteria outgrow the beneficial microbiota thus leading to illness. Furthermore, due to the depletion of beneficial bacteria, the host is also deprived of the benefits provided by them. This condition is termed as "Dysbiosis".[10]

Dysbiosis has been implicated in a wide range of diseases with GI origin as well as extra-GI origin. These diseases include diarrhea, inflammatory bowel disease (IBD), obesity, allergic disorders, type 1 diabetes mellitus, autism, obesity, and colorectal cancer. However, it should be noted that even in diseases of extra-GI origin, gut dysbiosis plays a significant role in the disease pathogenesis.[11]

2. Probiotics – Friends for life

The term "Probiotic" is derived from the Greek words "*Pro*" and "*bios*" meaning "for life".[12] The current definition of 'Probiotics' is given jointly by Food and Agriculture Organization (FAO) and World Health Organization (WHO). Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[13] Probiotic products may constitute of single or several microbial strains. Microbial strains belonging to the following genus: *Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus, Enterococcus, Bacillus,* and *Saccharomyces* are very widely used in many probiotic products.[14]

As probiotic properties have been shown to be strain specific, benefits and functions offered by one strain cannot be extrapolated to other strains without carrying out strain specific clinical trials.[15] Probiotic bacteria are proposed to benefit human health mainly by three general mechanisms of action which have been illustrated in Figure 1.

In the current era, other than the basic role of nutrition which is to supply essential nutrients for the growth and development of the body, additional aspects like maintaining good health, enhancing immunity and counteracting diseases are becoming important.

Extensive studies and clinical trials have been carried out on probiotics suggesting their use and benefit in literally every disease known to the humankind.

3. LGG^{TM} – A friend that's one of its kind

Dr. Sherwood Gorbach and Dr. Barry Goldin originally isolated a potential probiotic strain from the stool sample of healthy adult human in 1985. Owing to its stability in acid and bile medium, good growth characteristics and excellent adhesive property, the strain was patented and named "*Lactobacillus rhamnosus* GG (LGG^{TM}), ATCC 53103". GG in the name stands for the surname letters of doctors who isolated LGG^{TM}.[16]

The mechanism of action of LGG^{TM} and its properties have been illustrated in Table 1 and Table 2 respectively.

Since 1990, LGG^{TM} has been widely used in several probiotic products and probiotic supplements. In the field of probiotic research, LGG^{TM} is one of the best-studied probiotic in clinical trials. It has been reported in many clinical trials that LGG^{TM} exert effect in prevention and treatment of several disorders of GI as well as extra-GI origin.[17]

There are several commercially available LGG^{TM} products in the market world-wide. LGG^{TM} like other probiotics is usually available as lyophilized or heat dried granules/powder in sachets/capsules.[18]

3.1. LGG^{TM} – The right strain gives the right result

Selection of a high-quality probiotic strain is one of the important factors that determine the efficacy of the probiotic.[37] Some of the factors that determines the quality of a probiotic strain are mentioned below:

3.1.1. Manufacturing of the strain

Since probiotics are natural products, manufacturing and production of a high-quality probiotic strain is not a generalised procedure. Several variables exist during the manufacturing process which has to be controlled so as to obtain a high-quality probiotic strain.[38] Manufacturing high-quality probiotics on a large scale require unique

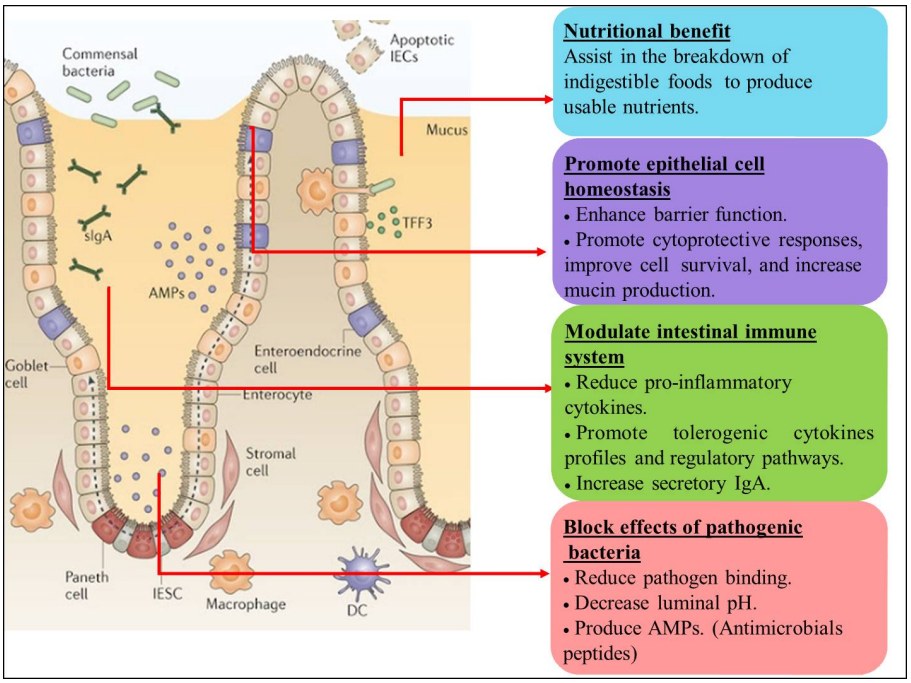

Fig. 1: General mechanisms of actions through which probiotic bacteria are proposed to benefit human health.

Table 1: Mechanism of Action of LGG^{TM}

Luminal Action	
Anti-microbial property	
1. Accumulation of lactic acid which acts by lowering the optimal pH and exhibiting its anti-microbial properties.	19
2. Production of Bacteriocin (with antimicrobial activity against anaerobic bacteria, such as *Clostridium, Bacteroides*, and *Bifidobacterium*, as well as *Escherichia coli, Pseudomonas, Staphylococcus, Streptococcus,* and *Salmonella*)	20
3. Production of seven heat-stable peptides (with antibacterial activity against entero-aggregative *E. coli* strain EAEC 042, *Salmonella* typhi, and *Staphylococcus aureus*)	21
Competitive colonization	
1. Suppression of pathogenic cell adherence that interferes with host bacterial colonization	16
2. SpaCBA pili mediated adhesion which is supposed to be strongest as compared to other probiotic bacteria.	22
3. LGG^{TM} also competes for gut monosaccharides and thus slows the growth of other potential pathogens in its vicinity. This has particular relevance to *Clostridium difficile.*	23
Trophic action	
1. LGG^{TM} promotes the survival of IECs by preventing cytokine-induced apoptosis through blocking of p38 mitogen-activated protein (MAP) kinase.	24
2. Production of Msp1 and Msp2. Each activates the Akt signaling peptide, inhibits cytokine-induced IEC apoptosis, and reduces TNF-induced epithelial damage.	25
3. Production of SCFAs which is the main source of energy for colonocytes, is involved in cellular apoptosis and NF-kB signalling that confers it anti-cancer and anti-inflammatory effects while also decreasing epithelial permeability by bacteria.	26,27
Regulation of Immune Response	
1. Lipoteichoic acid (LTA) as key immune effector of LGG^{TM}	28
2. Increases Immunoglobulins (IgG and IgA) levels	29
3. LGG^{TM} enhances Th1 responses, activating cell-mediated immunity	30
4. LGG^{TM} enhances pulmonary NK cell activity thus protecting subjects from influenza virus infection.	31

IEC: Intestinal epithelial cells, MAP: mitogen-activated protein, Msp: Major secreted protein,
TNF: Tumor Necrosis Factor, SCFA: Short Chain Fatty Acids, LTA: Lipoteichoic acid, Ig: Immunoglobulins, Th: T Helper,
NK: Natural Killer

Table 2: Properties of LGG^{TM}

1. LGG^{TM} has excellent adhesion capacity to mucosal cells versus other Lactobacilli.	32
2. LGG^{TM} encodes a genome that biosynthesizes a specific SpaCBA pili that play a key role in adhesion to mucosal cells	22
3. LGG^{TM} has the ability to survive and to proliferate at gastric acid pH.	33
4. LGG^{TM} has the ability to survive and to proliferate in medium containing bile.	33
5. Potentially owing to its excellent binding abilities, the organism can be cultured in saliva 2 weeks after ingestion, cultured from stool for 7 days, and cultured from intestinal biopsy specimens for 28 days.	34–36
6. The colonization capacity of LGG^{TM} is significantly better in new-borns. In addition to colonizing the small intestine preferentially, it also adheres well to the colon and can also be recovered from the oral cavity, tonsils, and vagina.	22

nutritional requirements and evaluation of different aspects that affects the manufacturing of strain. Development of a customized manufacturing process for a specific strain poses a challenge because of the various intricacies involved in the manufacturing process. Various procedures and steps are needed to be well understood and accommodated within the manufacturing process so as to yield a high-quality end product.[38] Therefore, the quality of these products from different sources may vary and many of the commercially available products may lack regulated quality control. The manufacturer in possession of the patented strain is the most proficient candidate to produce the high-quality strain. Therefore, selecting products from companies that manufacture the original LGG^{TM} strain may indicate higher degree of commitment to high-quality probiotic supplements.

3.1.2. Preservation of the strain

Also, the quality and integrity of the selected strain is ensured by preservation of the strain in a qualified cell-bank system.[39] Manufacturer of the patented strain is responsible to ensure that the strain is preserved suitably in a cell culture bank so that the characteristics and properties of the strain are sustained.

3.2. Generic probiotics: Boon or bane

LGG^{TM} is the most documented and widely studied probiotic strain with more than 1100 publications and approximately 300 human clinical trials in diseases of GI as well as extra-GI origin. After the expiry of the patent of LGG^{TM}, the complete genome sequence of *Lactobacillus rhamnosus* GG (ATCC 53103) was made available.[40] LGG^{TM} was then made freely available for the use of others and the claims of LGG^{TM} were linked to the generic LGG^{TM} (henceforth mentioned as 'generic GG') strains, similar to the theory of generic drugs.[41] Of late, a concept of "generic probiotics" was introduced. The concept is analogous to the concept of generic drugs. The intention behind this concept was to make the probiotics available for people belonging to the developing countries. After the expiry of the patent, the probiotic is introduced under a different brand name at nominal prices. Also the health and safety claims made by the patented probiotic can be extrapolated to the generic probiotics on the condition that the genome of the generic strain is identical to the genome of original strain.[42]

Due to the availability of generic probiotics, several products of generic GG have flooded the Indian market. In most of the countries, probiotics come under the category of dietary supplements or over-the-counter products. National drug regulatory authorities do not supervise the probiotic supplements and that is why very less clinical guidance is offered as compared to the prescription drugs.[43] This situation often leaves a healthcare professional confused with regards to the use of the original LGG^{TM} strain amidst plethora of generic GG strains products.

Probiotic effects are observed to be strain specific. Effects of one strain cannot be extrapolated to another strain. With the variation in strain, the efficacy of the strain to prevent or treat any condition will also differ substantially.[44] Keeping this in mind, it is essential to establish this notion that there is no generic equivalency between probiotic strains. Therefore, from the clinician's point of view, it is vital that they recommend or use original commercially available strains which have been specifically studied in clinical trials and have demonstrated noticeable benefits.[45]

3.3. Every GG is not LGG^{TM}

3.3.1. Pili – The vital organ of LGG^{TM}

One of the reasons why LGG^{TM} was granted the patent was due to its excellent adhesive property. LGG^{TM} has been widely studied with respect to its good mucus adhering capacity. LGG^{TM} has the excellent adhesive property by the virtue of SpaCBA pili. It has been demonstrated that LGG^{TM} harbours SpaCBA gene cluster which is involved in the biosynthesis of LGG^{TM}-specific SpaCBA pili. One of the most important component of the pili is the larger minor pilin SpaC located on the tip and the length of the pili, known to play a vital role in adhesion to the mucus.[46] Therefore, it is imperative that the LGG^{TM} strain should not be devoid of pili, so as to display excellent adhesive property

and exert its probiotic benefits to the humans.

Improper or invalidated manufacturing processes can lead to production of substandard probiotic product. It was demonstrated in a study that bacterial cells of LGG™ when subjected to 8000 x g centrifugal forces, lacks pili which is very vital in adhering to mucus. Thus, it is evident that LGG™ pili are predisposed to damage due to shearing stress. Since, pili are known to perform an important function of adhesion; detrimental shearing stress during manufacturing of LGG™ should be avoided.[47]

Several studies have tested the adhesive properties of original LGG™ strain and generic GG strains. It was found that the adhesive property of generic GG strains differs significantly as compared to original LGG™ strain. It was inferred that, the probable cause for the diverse adhesive properties in generic GG strains can be attributed to differences in the industrial production by different manufacturers.[32] Another thing that warrants serious consideration is that if adhesion is modified during industrial processes, could this mean that other probiotic traits may also be altered.

3.3.2. Genome stability – An essential parameter

Few years back, genetic drift was strongly linked in bacterial strains. Genetic drift can be defined as divergence via DNA mutation of a bacterial strain over time. DNA mutation takes place at a very low pace unless selection pressure is applied. This recent research with regards to genetic drift in bacteria suggests that there is a high probability of genetic drift occurring in probiotic strains as well. Probiotic manufacturers hence should address the risk of genetic drift in probiotic strains in their industrial processes. Strict and validated process control during the entire manufacturing process should be followed to ensure low potential for genetic drift.[48]

Another study carried out the comparative genome analysis of original LGG™ and generic GG. They investigated, to what extent the genome of LGG™ is stable in commercially available generic GG products. It was found that, major genetic rearrangements which include deletion of genes were observed in the generic GG strains. The missing gene includes SpaCBA which encodes for the pili which is responsible for the adhesion and persistence in the intestinal tract. However, quantitative polymerase chain reaction (qPCR) results confirmed the presence of SpaCBA pili in all the products containing LGG™ strain. The authors of the above study stated an imperious need for controlling and validating production processes of generic products so as to confirm genetic or genome stability in generic GG strains.[42]

3.3.3. Traits required for survival in the GIT

Various factors are found to affect the probiotic characteristics. Some of the common factors responsible for change in probiotic characteristics are the environmental factors encountered during manufacturing processing and the selection of variants through long-term subculturing.[32] Acid and bile tolerance are some of the important probiotic traits helping them to survive the harsh conditions of human GIT.[49] The probability of these traits getting affected during the invalidated and improper manufacturing process cannot be negated. Data showing the differences in acid and bile tolerance between LGG™ and generic GG strain is lacking.

To summarize, the basic differences in the original LGG™ strain and generic GG strain have been illustrated in Table 3.

3.4. LGG™ recommendations by health authorities

LGG™ has been widely reviewed in more than 1100 publications and studied in more than 300 human trials. It is also mentioned in Nelsons Textbook of Pediatrician which is considered as a go-to book by the Pediatricians and also in other textbooks as a therapy for treating pediatric acute gastroenteritis. It is also recommended by various health authorities all over the world in various diseases which are illustrated in Table 4.

4. Monostrain vs Multistrain probiotic

It has been demonstrated in multiple studies that a multistrain probiotic is more effective and consistent in showing their benefits as compared to monostrain probiotic. Colonisation of an ecosystem constituting of more than 400 species is anticipated to be more successful with multistrain, multispecies probiotic than with monostrain probiotics.[57] A probiotic preparation which offers greater diversity is projected to provide broad spectrum of probiotic efficacy. In that case, it is promising to use combination of probiotic strains belonging to different species and genera, and different strains from same genus, referred to as multispecies and multistrain, respectively.[58]

In 1992, after carrying out several experiments a group of probiotic experts gave a consensus statement which stated that ‘different strains can be targeted toward different ailments and can be blended into one preparation’. Mixed cultures contain multiple strains of bacteria that complement each other’s functional properties and thus give a collegial benefit.[59]

Probable mechanisms responsible for success of multistrain probiotic over monostrain probiotics are as given below:[60]

4.1. Successful colonisation

Survival of single strain is dependent on its own properties. The single strain has to overcome all the barriers on its own so as to establish itself in the gut of the host. Multiple strains with different characteristics support each other to

Table 3: Original LGG™ vs Generic GG

Differentiating parameter	Original LGG™	Generic GG
Logo	LGG™ and LGG® are trademarks of Chr. Hansen A/S.[50] Only products using the LGG™ strains are authorized to use the trademarks on label.	Generic GG marketers are not authorized to use the symbol of LGG™ or LGG®.
Acquired from	Chr. Hansen	Other than Chr. Hansen
Adhesion	SpaCBA pili always present and remain intact.	SpaCBA pili may or may not be present and intact.
Acid and bile stability	Acid and bile stability guaranteed	Acid and bile stability may not be guaranteed
Genome stability	Genome stability guaranteed	Genome stability may not be guaranteed

Table 4: LGG™ recommendations by various authorities world wide

Authority name	Recommendations
American Academy of Pediatricians (AAP)[51]	Antibiotic Associated Diarrhea
European Pediatric Association (EPA)[52]	Nosocomial Diarrhea
	Antibiotic Associated Diarrhea
	Acute Gastroenteritis
Canadian Pediatric Society[53]	Antibiotic Associated Diarrhea
	Acute Infectious Diarrhea
	Irritable Bowel Syndrome
	Preventing Infections
European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)[54]	Acute Gastroenteritis
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)[55]	
	Antibiotic Associated Diarrhea
	Infectious Diarrhea
	C. difficile Diarrhea
	Pouchitis
World Gastroenterology Organization (WGO)[56]	Acute Diarrhea
	Antibiotic Associated Diarrhea
	Nosocomial Diarrhea
	Adjuvant therapy for *H. pylori* eradication
	Irritable Bowel Syndrome

overcome barriers and hence have an enhanced chance at successful colonisation. The enhanced chances of successful colonisation are as a result of enhanced adhesion, creation of favourable environment by induction of optimal pH range, and reducing the antagonistic activity of endogenous microbiota.

4.2. Multiple health benefits

Every strain has specific probiotic properties which cannot be generalised to other strains. Administering multiple strains of probiotics gives the benefit of multiple properties which could prove beneficial for the host in ailments involving multiple pathologies. Positive interrelationship between multiple strains brings out the synergism which results into health promoting properties.

An analysis of multiple studies involving LGG™ as a single strain and as one of the component of the multistrain probiotics has drawn a conclusion that 60% of health targets were achieved with LGG™ in combination with other strains as compared to 51% of health targets achieved with LGG™ alone.[58]

From the various studies reviewed, there are decent evidences on multistrain probiotics exhibiting valuable properties against a wide range of ailments. The evidences show that multistrain probiotics are effective in disorders like acute diarrhea in children, Antibiotic Associated Diarrhea (AAD), Irritable Bowel Syndrome (IBS), etc.[61]

5. Clinical Trials on LGG™

LGG™ has been studied and experimented on diseases of GI as well as extra-GI origin. However its effect was greatly demonstrated in pediatric diarrhea, AAD, IBS and Necrotising enterocolitis(NEC). Table 5 summarizes some of the clinical trials in each of the above indication.

Table 5: Clinical trials of LGG^{TM} in various gastro-intestinal infections

S. No.	Clinical trial conducted by	Participants	Intervention(LGG^{TM} vs Placebo)	Outcome	
				Duration of diarrhea	Duration of Hospital stay
Acute diarrhea or acute gastroenteritis					
1	Canani RB et al.[62]	571 children aged 3-36 months.	LGG^{TM} (6 x 10^9Colony Forming Units (CFU) twice daily	Significantly shorter (P<0.001) in LGG^{TM} group vs ORS group [78.5 hrs vs115.0 hrs]	Decreased
2	Basu S et al.[63]	235 children	ORS + LGG^{TM} (1.2 x 10^9CFU once daily)	Significantly shorter (P< 0.05) in ORS+ LGG^{TM} group vs ORS+ placebo group [5.2 days vs 9.2 days].	Significantly shorter (P< 0.05)in ORS + LGG^{TM} group vs ORS+ Placebo group [7.3 days vs 15.5 days].
3	Basu S et al.[64]	559 children	ORS + LGG^{TM} (10^{10}CFU twice daily)	Significantly shorter (P=0.000)* in ORS+LGG^{TM} group vs ORS group [5.02 days vs 7.23 days].	Significantly shorter (P=0.000)* in ORS+LGG^{TM} group vs ORS group [6.21 days vs 9.75 days].
4	Aggarwal S et al.[65]	200 children aged 6 months - 5 years	LGG^{TM} (10^{10}CFU once daily)	Significantly shorter (P<0.001) in children in LGG^{TM} group vs placebo [60 h vs. 78 h].	NA
5	Guandalini S et al.[66]	287 children 1 month to 3 years of age	LGG^{TM} (at least 10^{10}CFU/250 ml)	Significantly shorter (P<0.03) in children in LGG^{TM} group vs placebo [110.4 h vs. 122.9 h].	Significantly shorter (P=0.04) in children in LGG^{TM} group vs placebo [80 h vs. 95 h].
6	Szajewska H et al.[67]	15 RCTs (2963 participants)	LGG^{TM} (< 10^{10}CFU per day and $\geq$ 10^{10}CFU per day)	Significantly reduced by 1.05 days in LGG^{TM} group vs placebo	NA
7	Szajewska H et al.[68]	Eight RCTs (988 participants)	LGG^{TM} dose ranging from 10^9-10^{11} CFU per day	Significantly reduced by 1.10 days in LGG^{TM} group vs placebo. In diarrhea specifically due to rotavirus: Significantly reduced by 2.1 days.	Decreased
Antibiotic associated diarrhea					
8	Vanderhoof JA et al.[69]	188 children between 6 months and 10 years of age	LGG^{TM} 10^{10} - 2 x 10^{10} CFU per day	Reduction in the incidence in LGG^{TM} vs placebo group [7 children vs 25 children]	

Continued on next page

Table 5 continued

9	Szajewska H et al.[70]	12 RCTs (1499 participants including children and adults)	LGG^{TM}- 4 x 10^8 - 12 x 10^{10}CFU per day	Significantly reduced risk of AAD in LGG^{TM} vs placebo group [22.4% vs 12.3%]RR=0.49
10	Arvola T et al.[71]	119 children from 2 weeks to 12.8 years of age	LGG^{TM}- 2 x 10^{10}CFU twice daily	Significantly reduced incidence of AAD in LGG^{TM} vs placebo group [5% vs 16%]P=0.05
11	Armuzzi A et al.[72]	120 *H. pylori* infected adults on triple therapy	LGG^{TM}- 6 x 10^9CFU twice daily	Significantly reduced incidence of AAD in LGG^{TM} vs placebo group [6.6 % vs 23.3 %]RR=0.3
Irritable Bowel Syndrome				
12	Francavilla R et al.[73]	141 children	LGG^{TM}- 3 x 10^9CFU twice daily	Significant reduction in the frequency (P<0.01) and severity (P<0.01) of abdominal pain
13	Pedersen N et al.[74]	123 patients (age range: 18-74 years)	LGG^{TM}- 6 x 10^9CFU twice daily	Significant reduction (P<0.01) in IBS-SSS from baseline in LGG^{TM} vs placebo group [68 vs 133]
Necrotizing enterocolitis				
14	Uberos J et al.[75]	261 neonates aged 27-32 weeks.	LGG^{TM}- 10^9 CFU /day	LGG^{TM} supplementation in VLBW infants has been associated with lower frequency of NEC$\geq$ Stage II , fewer cases of sepsis and low mortality
15	Manzoni P et al.[76]	80 preterm neonates with a very low birth weight	LGG^{TM}- 6 $\times$ 10^9 CFU/day	LGG^{TM} significantly reduces the incidence and the intensity of enteric colonization by *Candida* species
Trials on multistrain probiotics				
16	Grenov B et al.[77]	400 children suffering from diarrhea	LGG^{TM} + BB-12, 5 x 10^9 CFU each per day	Significant reduction in duration of diarrhea by 2.2 days. (P=0.025)
17	de Vrese M et al.[78]	88 *H. pylori* infected adults on triple therapy	LA-5 and BB-12 (1.2 x 10^9 CFU each) twice daily	Significant reduction in the duration of AAD in probiotic vs placebo [4 days vs 10 days] (P<0.05) and improvement in gastrointestinal complaints (P<0.05)
18	Chatterjee S et al.[79]	Adults with 7-day course of oral antibiotic	LA-5 and BB-12	Significantly shorter duration of diarrhea (P=0.01) in probiotic group vs placebo [2 days vs. 4 days].
19	Fox MJ et al.[80]	70 children (1-12 years) prescribed with antibiotics	LGG^{TM} (5.2x 10^9 CFU), LA-5 (8.3x 10^9 CFU), BB-12 (5.9x 10^9 CFU) per day	Significantly lower (P<0.001) episodes of diarrhea in probiotic group vs placebo [1 episode vs 21 episodes]

ORS: Oral Rehydration Salts, CFU: Colony Forming Units, AAD: Antibiotic Associated Diarrhea, IBS-SSS: Irritable Bowe Syndrome Severity Scoring System, NEC: Necrotising Enterocolitis, VLBW: Very Low Birth Weight, LA: *Lactobacillus acidophilus*, BB: Bifidobacterium, *: Statistically highly significant

6. Conclusion

Currently, probiotics are best considered as therapeutic adjuncts to ease or lower the symptoms associated with various disorders especially the ones related to gastro-intestinal tract, shorten the duration of disorder and maintain overall health.

It is indispensable to be familiar with some of the basic facts about probiotics. First and foremost, not all probiotics are same. Probiotics differ in various parameters like their physiological and microbiological characteristics, clinical effects they exhibit, dose required to attain these clinical effects and to what extent the clinical properties of the probiotic has been studied in clinical trials. Different strains of same species of probiotic differ with respect to aforementioned parameters. Moreover, some of the marketed products claiming to be probiotics are not in actual probiotics because there is dearth of evidence to support the efficacy of a particular strain used. Selection of a probiotic strain for an ailment should be based on clinically demonstrated benefit in that ailment.

The field of probiotics is evolving rapidly and the physicians are mandated to stay up-to-date by being cognizant about novel studies that set forth new recommendations. They should also be cautious of the companies that follow the bandwagon without adequate data to support their product. These products might not be beneficial, but the notion could be ruled out by conducting trials to test their efficacy.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare no conflict of interest

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