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Uses of Probiotics and Immunonutrition in Gastrointestinal Disorders – Recommendations and Practices

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Abstract

Probiotics play a key role in restoring the normal gut microbiota and improves the gastrointestinal function. Generally, probiotics are pondered to be dietary factors which have an impact on the gut microbiota and to have a monitoring effect on the intestinal flora. The gut-liver axis has a pivotal role in the liver disease pathophysiology. Immunonutrition uses nutritional interventions to produce health-related effects beyond the primary nutrient value and regulate the neuroendocrine immunoinflammatory responses. Few studies are favouring the use of probiotics and immunonutrition in gastrointestinal disease. Still not much evidence-based guidelines pertaining to the uses of immunonutrition and probiotics are available. This article will provide an overview of the current practices and guidelines in the use of probiotics and immunonutrients in gastrointestinal diseases.

Keywords: Probiotics; Immunonutrition; Gutliver axis; Gut microbiota; Sarcopenia

Introduction

Probiotics are live organisms, particularly bacteria intended to have health advantages if consumed in an appropriate quantity [(1)]. Probiotic use is not a novel entity. Millions of humans use probiotic dietary supplements to improve their digestive health. Probiotics, fermented foods are part of vitamins in South Indian food tradition. The benefits of probiotics, either with one strain or multiple/combined strains of probiotics, have been checked in patients with diarrhoea due to antibiotic use, colitis due to "Clostridium difficile, infectious diarrhoea, Ulcerative colitis, Crohn's disease, and irritable bowel syndrome, and other disorders".

The liver plays pivotal function in detoxing and in substrate metabolism. It is obvious that the composition of bacterial components in the intestine may want to affect the functioning of the liver [(2)]. Few studies showed probiotics are powerful, however at the same time, one study reported that many human being's digestive tract prevent normal probiotics from efficaciously colonizing bacteria [(2)].

The "gut–liver" axis has a huge function in the pathophysiology of numerous hepatic diseases[3]. Probiotics enables to modulate the immune system in the intestine via luminal conversion process[4]. Probiotics may additionally alter gut microbiota and may change pathogenic interactions in chronic liver disease[4,5]. They might also repair the composition of the intestine microbiome and induces beneficial features to gut microbial communities resulting in enhancement or prevention of intestinal inflammation and different intestinal or systemic diseases[6]. The impact of gut microbiota on immune system of a person is enormous. Gut microbiota can sustain the mucosal barrier integrity, supply nutrient components, and fight microorganisms[7].

Mechanism of action/ uses of probiotics

1. Act as a barrier by increasing epithelial barrier function.
2. Inhibit the pathogenic microorganisms.
3. Gastrointestinal immunity modulation
4. Modification of gut microbiota & Regulation of intestinal microbiota.

Enhancing epithelial barrier function by probiotics

Intestinal epithelial barrier integrity is essential for maintaining the homeostasis of mucosal function, and helps to increase the absorption of nutrients. The mucosal epithelial barrier can be challenged by encounters with bacterial or viral pathogens. The foremost drug-resistant barrier is the mucosal barrier which combat with infective pathogens after they enter the intestine.

The bodily fluid layer, the epithelial coating of mucosal tissues, as well as the resistant cells in the subepithelial layer are parts of the mucosal boundary. Microorganisms must cross the mucosal obstruction before they arrive at the epithelium. It very well may be construed that bodily fluid substance and primary changes could influence barrier capability. Investigations have discovered that unsafe microorganisms in the gut can create specific explicit substances to vitiate the mucus, in this manner impairing human wellbeing[8].

Augmented permeability of mucosa and disruption in the epithelial mucosa can play a key role in the pathogenesis of many "gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD)", metabolic syndrome (obesity) and necrotising enterocolitis (NEC)[9]. Probiotics can improve the intestinal epithelial barrier and can modulate intestinal mucosal function, thus improving health status by augmenting the mucus secretion by goblet cells (Figure 1). Probiotics augments the IgA levels in IgA secreting cells in the "lamina propria" and increase the secretory IgA into the luminal mucous layer and helps to maintain the epithelial barrier function. For example, probiotic "*L. plantarum* BMCM12" safeguard the intestinal barrier by secreting extracellular proteins and diminish the pathogenic adhesion. The metabolites of probiotics such as butyric acid exerts beneficial effects in maintaining the epithelial barrier[10]. Previous studies reported that probiotics lessens the permeability of intestine and protect the gut[8]. Few studies reported that VSL#3, a probiotic mixture can intermingle with epithelial cells in the intestine and aid to sustain the epithelial mucosal barrier integrity[11–13].

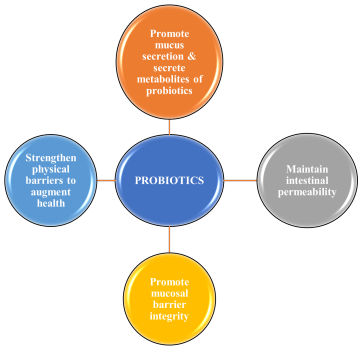

Fig 1. Epithelial barrier function by probiotics

Inhibit the pathogenic microorganisms

Human intestine harbors a huge number of microorganisms including harmful and beneficial organisms and probiotics. These pathogenic or harmful microorganisms can change the gut microbiota homeostasis and impose a major risk of developing GI diseases[14]. The action of probiotics on inhibiting the pathogenic organisms are illustrated in Figure 2.

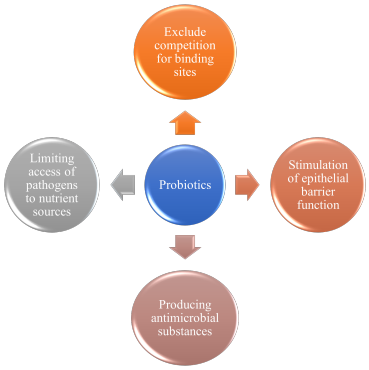

Fig 2. Inhibiting pathogenicaction by probiotics

Modulation of gastrointestinal immunity

Recent findings highlighted that probiotics (live) and their metabolites can exert immunoregulatory functions[15–17]. Modulation of immune system by probiotics use is depicted

in Figure 3. More research studies are required to explore the action of probiotics on maturation of gastrointestinal immunity.

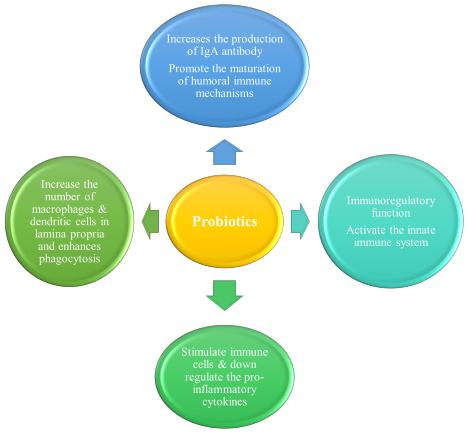

Fig 3. Modulation of gastrointestinal immunity by probiotics

Modification of gut and intestinal microbiota

Probiotics can regulate the gut microbiota composition and aid in inhibition of intestinal pathogenic bacterial colonisation and augments the immunity and maintain the integrity of mucosal layer of intestine. Modulation of gut microbiota by fermentation of nutrients and thus acidifying the colon and enhances immunity.

- **Commonly used Probiotic strains for adults** [18–20]
  - *Bifidobacterium spp*. (*B. breve* SD5206, *B. bifidum* CUL20, *B. infantis* SD5220, *B. lactis* CUL34, *B. longum* SD5219, *B. longum infantis* 35624)
  - *Escherichia spp.* (*E. coli Nissle* 1917)
  - *Lactobacillus spp*. (*L. acidophilus* CL 1285, CUL21, CUL60, SD512, *L. bulgaricus* SD5210, *L. casei* LBC80R, SD5218, *L. helveticus* R0052, *L. paracasei* 8700:2, *L. plantarum* 299v, HEAL9, SD5209, *L. reuteri* ATCC 55730, ATCC PTA 5289, DSM 17938, NCIMB 30242, *L. rhamnosus* CLR2, GG, R0011.
  - *Saccharomyces spp.* (*S. boulardii lyo*, *S. cerevisiae* I-3856)
  - *Streptococcus spp.* (*S. salivarius* K12, *S. thermophilus* SD5207)
- **Probiotics in the management of gastrointestinal disorders.**

The World Gastroenterology Organization, 2011 [18] formulated guidelines for the use of probiotics and prebiotics in adults and children Table 1. The diseases are [21]

- "Antibiotic-associated diarrhoea"
- "Irritable bowel syndrome"
- "Inflammatory bowel disease"
- *Helicobacter pylori* infection.
- Traveler's diarrhea
- Other diarrheal diseases are "IBD, celiac disease, and lactose intolerance".

Role of Probiotics in Liver Diseases

Hepatic Encephalopathy

The "gut-brain axis" is portrayed by complex bidirectional correspondence between the stomach and mind to keep up with gastrointestinal homeostasis and impact mental functions. Dysbiosis of the gastrointestinal microbiota adjusts the microenvironment of the colonic lumen, particularly the pH, which adds to enhanced production of ammonia from the stomach microbiota and enhanced absorption of ammonia from the colonic lumen to the blood. A few studies have affirmed that probiotics are successful and safe, are negligibly harmful, and have not much adverse impacts in the management of Minimal Hepatic Encephalopathy (MHE) [22].

While comparing with lactulose, probiotics are linked with less side effects and are well tolerated. A recent study examined the effects of a probiotic mixture consisting of *Bifidobacterium infantis* and *Clostridium butyricum* on patients with MHE with the intention of developing a new clinically applicable adjuvant therapy for MHE [23].

Alcoholic Hepatitis

Despite the fact that alcohol is mainly metabolized in the liver and it is notable that alcohol ingestion causes gut lumen bacterial abundance and dysbiosis, digestive tract mucosal alterations, and enhanced gastrointestinal penetrability, prompting enhanced translocation of microbes and their by-products, endotoxin (chiefly lipopolysaccharide, LPS), into the portal circulation. Bacteria and their products accelerate the creation of ROS and proinflammatory cytokines and chemokines, lead harm to hepatocytes and the advancement of liver injury [24]. Gut microscopic organisms determined endotoxin acts through certain pattern identified receptors, for example, toll like receptors (TLRs) which are communicated in liver occupant macrophages, Kupffer cells, as well as other tissue types in the liver. It has been generally shown that alcohol ingestion prompts endotoxemia [25]. These perceptions recommend that gut microbes homeostasis, gastrointestinal barrier integrity, and hepatic TLRs are significant in the pathogenesis of ALD.

Non-Alcoholic Steato-Hepatitis

A wide range of pathological hepatic conditions, from simple steatosis to non-alcoholic steatohepatitis (NASH), which may predispose to liver cirrhosis and hepatocellular carcinoma (HCC), make up non-alcoholic fatty liver disease (NAFLD). Because of the high incidence of obesity, NAFLD is addressing

Table 1. The World Gastroenterology Organization, 2011 guidelines for the use of probiotics in adults with level 1 evidence [18]

Disease	Probiotic strain
Acute diarrheal management	• *Enterococcus faecium* LAB SF 68 • *Saccharomyces boulardii*, strain of *S. cerevisiae*
Clostridium \difficile diarrhea prevention	• *L. casei* DN-114 001 in fermented milk • *L. acidophilus* CL1285 + *L. casei* LBC80R • *S. boulardii*, strain of *S. cerevisiae*
Antibiotic-associated diarrheal prevention	• *Enterococcus faecium* LAB SF 68 • *S. boulardii*, strain of *S. cerevisiae* • *Lactobacillus rhamnosus* GG • *L. casei* DN-114 001 in fermented milk • *L. acidophilus* CL1285 + L. casei LBC80R
Helicobacter pylori eradication - Coadjuvant therapy	• *L. rhamnosus* GG • *Bacillus clausii* (Enterogermina strain) • *S. boulardii*, strain of *S. cerevisiae* • *L. reuteri* ATCC 55730
Reduction of symptoms associated with lactose maldigestion	Yoghurt with live cultures of • *L. delbrueckii* subsp. *bulgaricus* and • *Streptococcus thermophilus*
Relief of symptoms of irritable bowel syndrome (IBS)	• *Bifidobacterium infantis* 35624 • *Bifidobacterium animalis* DN-173 010 in fermented milk • *L. rhamnosus* GG, • *L. rhamnosus* LC705, • *Bifidobacterium breve* Bb99, • *Propionibacterium freudenreichii* spp. *shermanii*
Remission maintenance in ulcerative colitis	• *Escherichia coli* Nissle 1917
Mildly active ulcerative colitis or pouchitis - Treatment	• VSL #3 mixture of eight strains • (1 *S. thermophilus*, 4 *lactobacilli*, 3 *Bifidobacterium*)
Prevention and maintenance of remission in pouchitis	
Prevention of common infections in athletes	• *L. casei* Shirota in fermented milk

a worldwide medical problem and the main source of liver injury around the world. Currently, there are no therapeutic interventions for the prevention and management of NAFLD, with the exception of lifestyle, diet, and exercise changes, which have disappointing results due to patients' poor compliance.

Numerous studies demonstrated that probiotics administration might attenuate NAFLD features in animal models [26]. The organization of VSL#3, a combination of three genera of microorganisms (a multistrain made by Streptococcus, *Thermophilus* and a few types of *Bifidobacterium* and *Lactobacillus*) for quite some time to Lep$^{ob/ob}$ mice further developed insulin responsiveness, complete unsaturated fat substance, serum alanine aminotransferase (ALT) levels and the histological range of liver injury [26]. The fact that Lep $^{ob/ob}$ mice exposed to VSL#3 had lower levels of uncoupling protein (UCP)-2 expression and less Jun N-terminal kinase (JNK) and NF-kB activation supported the hypothesis that intestinal bacteria may regulate the activation of host signalling pathways that interfere with hepatic insulin response and fat metabolism [26].

The impacts of probiotics as a mix of multistrain compounds have arrived at improved results in randomized trials. Most recently, Gao and collaborators showed that probiotics work on the clinical results of NAFLD patients, affecting insulin response and diminishing TNF-α. However, probiotics only reduced dyslipidemia in the Italian and Spanish populations, indicating that the effects of these molecules on HDL, LDL, and triglycerides may be influenced by ethnic background [27].

Potential Role in Sarcopenia and Frailty of Cirrhosis

Liver decompensation causes less nutritional consumption and metabolic changes characterized by accelerated calorie utilization, less glycogen storage, elevated starvation reaction, and protein catabolism, promoting wasting of fat and muscles [28]. Sarcopenia represents a significant reduction of skeletal muscle volume and muscle function. Sarcopenia is linked with unfavourable outcomes in chronic liver disease (CLD). Sarcopenia is defined when the patient has less muscle mass and decreased HGS. Sarcopenia has great impact on activities of daily living, quality of life and functional abilities among older populations and in patients with liver diseases. Hence monitoring and assessment of level of nutrition and sarcopenia among cirrhosis patients is of utmost importance and special care has to be given to measure muscle mass and muscle strength [29]. Sarcopenia in patients with liver cirrhosis (LC) has been drawing in much consideration these days as a result of linkage to unfavourable results. LC can be connected with sarcopenia because of protein metabolic issues and energy metabolic problems. LC is related with significant changes in gut microbiota and injure at various degrees of protective sys-

tems of the digestive tract.

Gut microbiota has a prominent role in liver ailment pathogenesis. Supplementation of probiotics can be a secure and cost effective approach in the liver disease management [30].

Immunonutrition

Immunonutrition encompasses triggering our body's immune system through the intake of specific nutrients. Immunonutrition uses nutritional interventions to produce health-related effects beyond the primary nutrient value and regulate the neuroendocrine immunoinflammatory responses. Immune Modulating Formulations or immunonutrient are nutritional supplements with arginine, glutamine, nucleotides, omega-3/6 fatty acids, sulphur containing amino acids and antioxidants (Figure 4).

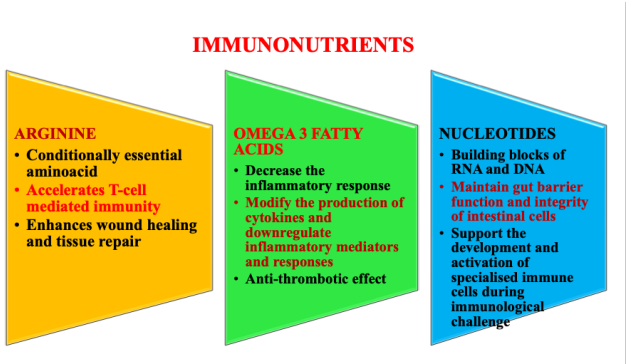

Fig 4. Components of immunonutrients and its uses

Role/Uses of immunonutrition in GI diseases

1. Down regulation of pro-inflammatory cytokines and inflammatory responses
2. Augments nutritional status
3. Shortens length of hospital stay after surgery and liver transplantation
4. Reduces post operative infectious complications
5. Decreases morbidity and mortality
6. Improves survival and clinical outcome
7. Enhances immunity
8. Improves liver function and decreases liver injury
9. Enhances liver regeneration
10. Improves gut epithelial barrier function
11. Enhances wound healing and decreases surgical wound complications

In a recent study recommended the significance of early nutritional planning with nutritional counseling among patients with end stage liver disease patients waiting for liver transplant to improve the clinical outcomes and liver function and the use of immunonutrient didn't show any statistically significant difference in liver function, but had showed some clinical improvement [31].

Recommendations

Recommendation 1 - Nutritional status Assessment/Screening

Nutritional screening/assessment to be performed on all patients with Gastrointestinal disorders at the time of diagnosis or their visits during OPD and/ within 24 hours of admission and thereafter on a regular basis.

- **Supporting findings**

A recent study revealed that 45% of patients with GI diseases were malnourished. Hence, it is very essential to detect and manage malnutrition in patients with gastrointestinal disease as it will influence the patient's clinical outcome and health care costs [32].

Recommendation 2 - Use appropriate tools for malnutrition assessment

Global Leadership Initiative on Malnutrition [GLIM] in 2016 with ESPEN recommended 'three phenotypic criteria' (non-volitional weight loss, decreased body mass index, and less muscle mass) and 'two etiologic criteria' (less food intake, and inflammation or disease burden). The diagnostic criteria for malnutrition are the presence of at least one phenotypic and one etiologic criterion. Phenotypic criteria are used for assessing malnutrition as 'stage 1 (moderate)' and 'stage 2 (severe)'. The etiologic criteria are intended for planning nutritional intervention and expected clinical outcomes [33]. CLD patients have less capacity to bear protein and PEM is corresponded with lack of vitamin A, zinc and magnesium.

- **Recommendation - 2a**
  - Guidelines provided by ESPEN recommended to use the RFH-NPT (Royal Free Hospital-Nutritional Prioritizing tool) to detect risk of malnutrition among patients with hepatic diseases.
  - SGA (Subjective Global Assessment) was commonly used to assess level of nutrition specifically for CLD candidates waiting for liver transplant [34,35].
  - The NRS-2002 (Nutrition Risk Screening) is a simple and well-validated tool, used most often in hospitals.
  - The Malnutrition Universal Screening Tool (MUST) used to identify malnourished individuals in all care settings.

Recommendation 3 - Use of Probiotics in GI diseases

- **3a**- The World Gastroenterology Organization, 2011 guidelines for the use of probiotics in adults with level 1

evidence [18].

- **Supporting findings**
  - Act as a barrier by increasing epithelial barrier function [8–10], [11–13].
  - Inhibit the pathogenic microorganisms [14].
  - Gastrointestinal immunity modulation [15–17].
  - Modification of gut microbiota & Regulation of intestinal microbiota [18–20].

- **3b – "Do not recommend the addition of glutamine, probiotics, or other supplemental nutrients to the diet in the aim of promoting the intestinal rehabilitation process (R39, Grade of evidence: low)" – ESPEN 2021 [36].**

Probiotics have not been tested for use in SBS (short bowel syndrome) rehabilitation. A few articles have portrayed the utilization of probiotics in SBS for treating D-lactic acidosis [37].

Recommendation 4 - Use of Immunonutrition in GI diseases

- "Peri or at least postoperative administration of specific formula enriched with (arginine, omega-3-fatty acids, ribonucleotides) should be given in malnourished patients undergoing major cancer surgery (B). There is currently no clear evidence for the sole use of these formulas enriched with immunonutrients vs. standard oral nutritional supplements (ONS) in the preoperative period (0)". ESPEN 2021 [38].

"Grade of recommendation B/0 e consensus (89% agreement)"

- "Immune modulating ONS including (arginine, omega-3 fatty acids, and nucleotides) can be preferred (0) and administered for five to seven days preoperatively (GPP).

Grade of recommendation 0/GPP e majority agreement, 64% agreement" [38].

Conclusion

More evidences are required to make a general recommendation for the use of probiotics and immunonutrition in gastrointestinal diseases. Many research findings support the use of probiotics and immunonutrients and have showed beneficial effects in improving clinical outcomes.

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