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A Comprehensive Perspective of Probiotics and their Significant Role in Successfully Preventing or Treating Diseases in Both Preventive and Clinical Medicine

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ABSTRACT

The aim and scope of this research/review article is to point out the role of probiotics and their immunomodulins to prevent or treat several incurable, acute and chronic metabolic diseases. The article is written to address physiological role of probiotics to prevent or treat such diseases at a molecular level, to safeguard humanity. It is also the aim of this research/ review article to educate the healthcare professionals on therapeutic aspects of several strains of probiotics, so that they can properly select them to treat their patients with greater efficacy.

This review and research article provides a comprehensive analysis of probiotics, with particular emphasis on their applications and significance in preventive and clinical medicine. The discussion encompasses morphology, cellular functions, distribution and predilection sites of the attachment of probiotics in the human gastrointestinal tract. In addition, definitions, regulatory considerations, and the therapeutic functions of various individual probiotic strains across different genera and species are presented with explicit details. Special attention is given to the biochemical mechanisms underlying the therapeutic effects associated with the prevention or treatment of specific diseases and symptoms, by individual probiotic strains present in multiple mixed strain culture. A major focus is placed on the role of probiotics in the prevention and treatment of hospital-acquired (nosocomial) infections, certain cancers, and several viral infections, with particular emphasis on the recent COVID-19 pandemic caused by the SARS-CoV-2 RNA coronavirus. The article offers a logical explanation of how probiotics may help modulate cytokine storms, a key factor in viral and bacterial infections, several allergies, obesity, and autoimmune disorders. During the course of research aimed at combating COVID-19, several serendipitous findings emerged, revealing potential therapeutic applications of probiotics in managing common conditions such as hypertension and type 2 diabetes. A scientific rationale is presented to explain the pathophysiology of these diseases and how probiotics may offer a novel approach to their treatment. Consequently, a concise pathophysiology of a particular disease has been presented to show exactly and hypothetically at what stage probiotics exert their therapeutic effect, for the sake of better understanding and appreciation by the readers. The article proposes function-specific combinations of probiotic strains that may serve as therapeutic agents for particular diseases or syndromes, offering a practical guide for physicians in clinical settings. The research/review article, presented with simplified and yet detailed schematic and pictorial presentation is an early guide to follow the theme of genesis, physiology, and role of probiotics to be used as preventative or therapeutic aids to prevent or cure several diseases in preventive or clinical medicine set up. For the sake of simplicity more emphasis has been placed on the pictorial presentations than elaborate and complex script for the sake of easy understanding, along with the pertinent references in this article.

Keywords: Multiple mixed strain probiotic therapy; Probiotics; Bacteriocins; Immunomodulins; Immunomodulation; Cytokine storm; COVID-19; Diabetes; Hypertension; Thrombosis; Anti-ageing; Allergy; Hospital-acquired infections; Nosocomial infections; Autoimmune diseases; Fecal microbiota therapy; SARS CoV-2; C.*diff*; MRSA; Immune checkpoint cancer therapy; Standard cancer therapy; Adjuvant cancer therapy; US Patent 11,077,052B1; Dysbiosis.

Introduction

Recently, it has been brought to the attention of people around the world by several medical professionals that allopathic medicines developed and recommended by pharmaceutical companies are causing serious, damaging side effects. These side effects can often be worse than the original disease itself. For decades, antibiotics have been used to treat bacterial infections, but now pathogenic bacteria have evolved to be multi-antibiotic resistant, causing hospital-acquired infections (nosocomial infections) that do not respond to antibiotics. According to an analysis, these infections are projected to kill over ten million people per annum by the year 2050.

Another devastating disease, cancer, has become a major subject of discussion among scientists and physicians. Due to a lack of proper treatment and modern scientific advancements, only 20% to 30% of cancer victims survive the disease. The relapse of cancer is a constant threat, and there is no permanent guarantee that a patient will be cured.

In addition, highly-mutated viruses like the SARS-CoV-2 virus which causes COVID-19, are spreading at a faster pace and causing pandemics. These pandemics have resulted in a severe loss of human lives and have drained the global economy. There is no specific treatment for viral diseases other than treating symptoms. Billions of dollars are spent annually on vaccinations and medications for viruses like the influenza virus, with limited success.

The human race has also been affected by other uncontrollable metabolic diseases such as hypertension, diabetes, obesity, food intolerances, and allergies. These conditions result in severe costs, a loss of time, and great stress on victims, their families, and governments. It has been shown that due to modern living, food habits, lifestyle, and severe stress, the human immune system has been compromised. It has also been reported that apparently modern pharmaceutical prescription drugs and over-the-counter drugs are not able to cure diseases with a high degree of accuracy and come without any side effects.

Thus, there is a great need for all-natural therapies to be used either as primary therapeutic agents or as adjuvants alongside standard treatments. One such emerging area is the use of natural probiotics to treat several diseases, as they can enhance immunity and orchestrate the human immune system through immunomodulation.

Before I proceed to discuss the role of probiotics to prevent or cure several diseases, I would like to provide a brief description regarding the genesis and evolution of these all-natural biological therapeutic agents.

Life on Earth is believed to have originated over 3.5 billion years ago, with the first major biological innovation being the production of oxygen through photosynthesis by primitive algae. This pivotal development laid the foundation for the evolution of more complex life forms, including unicellular bacteria and eventually multicellular organisms. Over time, the plant and animal kingdoms evolved, leading to the emergence of primates and, eventually, human beings.

If we consider the interconnectedness of all life forms, it becomes evident that microbial life has played — and continues to play — a foundational role in maintaining ecological balance. Based on current scientific speculation, bacteria first appeared around 3.0 billion years ago. Their emergence would have been followed by the evolution of viruses, which arose to maintain ecological equilibrium.

Despite their longstanding existence, bacteria remained unknown to humans until the invention of primitive microscopes. The Dutch lens maker Anton van Leeuwenhoek, in the late 1600s, was the first to observe microscopic organisms — later identified as bacteria — using handcrafted lenses. Although this marked the first visual confirmation of microbial life, little was understood about its implications, yet he became known as Father of Microbiology.

The turning point in the better understanding of bacteria came in 1865 with Louis Pasteur's germ theory. Although several other scientists worked on bacteria before, Pasteur was credited with Father of Bacteriology. He demonstrated that specific microorganisms were responsible for certain diseases and pioneered the process of milk pasteurization — heating milk to 161°F (72°C) for 15 seconds — to eliminate pathogenic bacteria and ensure safety for human consumption .In this connection, it is also worthwhile to mention that Robert Koch was credited as a pioneer in medical microbiology due to his discovery of Anthrax Bacillus in 1876, and also due to his famous Koch's postulates.

However, at that time, the focus remained on pathogenic bacteria, and the concept of "beneficial bacteria" was unknown. This changed with the pioneering work of Dr. Elie Metchnikoff, who in 1907 proposed that certain rod-shaped bacteria, particularly those originating from fermented milk, could prevent intestinal putrefaction and thereby enhance human longevity. He named these bacteria Lactobacillus because they appeared as rods (Bacillus) and are associated with milk (lacto).

Despite Metchnikoff's Nobel Prize being awarded for his work on phagocytosis rather than probiotics, his observations laid the groundwork for future research in the field and thus he was considered as Grand Father of Probiotics. Meanwhile, in ancient cultures — notably in the Indian subcontinent — the use of fermented milk products had been common for millennia. Indian scriptures (the Vedas) reference the consumption of fermented milk as far back as 5,000 years, attributing the practice to divine figures such as Lord Krishna. Thus, Lord Krishna can be named as Great Grand Father of Probiotics. Each household traditionally prepared and consumed these products daily, intuitively recognizing their health benefits without knowledge of the underlying microbiological mechanisms.

It was not until 1965 that the term **"probiotic"** was formally introduced by Lilly and Stillwell,[1]derived from

the Greek *"pro"* (for) and *"bios"* (life), in contrast to **antibiotics** (*"anti"* = against, *"bios"* = life). In 1974, Parker defined probiotics as "organisms and substances which contribute to the intestinal microbial balance."[2] Fuller (1989) refined this to "live microbial supplements which beneficially affect the host by improving its intestinal microbial balance." Salminen and colleagues in 1998 broadened the definition to include "foods containing live bacteria beneficial to health."[3]
The current widely accepted definition, developed jointly by the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO), states:

"Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host."[4,5] This comprehensive definition encapsulates all non-pathogenic, health-promoting microbes used in food and therapeutic applications.
In this connection it is worthwhile to mention the definitions of Para probiotics, postbiotics, immunomodulins, and prebiotics, since these terminologies are widely used in connection with probiotics, although they are physiologically different from probiotics.

Para probiotics refer to non-viable (dead) probiotic microorganisms that retain the ability to modulate or stimulate the immune system. Despite being inactivated, these microbes can still exert significant biological effects.

Postbiotics are the soluble byproducts or metabolites produced during the growth and metabolism of probiotics. These include substances such as lactic acid, bacteriocins, short-chain fatty acids, bioactive peptides, hydrogen peroxide, and other antimicrobial and immunomodulatory compounds. These postbiotics are also known as immunomodulins due to their role in influencing immune function.

Prebiotics, on the other hand, are not microbes or microbial products. Instead, they are substrates — typically dietary fibers — that are selectively utilized by host probiotic microorganisms to promote their growth or activity. Examples include inulin, oligosaccharides and various soluble and insoluble fibers that humans cannot digest but which serve as nourishment for beneficial bacteria in the gastrointestinal tract.

What is well-established in scientific literature is that probiotics, para probiotics and postbiotics all possess significant health-promoting properties, particularly in supporting digestive health, enhancing immune responses and maintaining microbial balance in the gut.
I'd also like to explore some of the health benefits of probiotics, para probiotics and postbiotics.

Functions of Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host. Their well-documented functions include reduction of lactose intolerance; immunomodulation and immune system stimulation; direct inhibition of pathogenic bacteria and viruses; enhancement of intestinal peristalsis and motility; reduction of blood cholesterol; reduction of the risk of certain cancers; and modulation of blood pressure and blood sugar levels.

Roles of Para-Probiotics and Postbiotics

Para probiotics (non-viable microbial cells) and postbiotics (metabolic soluble byproducts of probiotics) share many of the same health benefits as live probiotics, except for the direct inhibition of pathogenic microorganisms. However, they still enhance immune response and modulate immunity, indirectly contributing to the control of harmful bacteria and viruses.

In this connection, it is worthwhile to mention that Dr. Malireddy S. Reddy and Dr. D.R.K. Reddy were the first to introduce (in the world) probiotics as an essential therapeutic ingredient in combination with the drugs to enhance the drug efficiency to treat diseases with least side effects. A US patent # 6,080,401 and other international patents were granted in the year 2000 for their breakthrough invention.

Although probiotics have been part of human diets for thousands of years, the scientific community only began exploring them in earnest in the late 20th century. As of 2025, the term "probiotic" has been in use for just 60 years. Despite their ubiquity in public discourse and growing media attention, a deep understanding of their physiological and therapeutic potential remains limited — even among healthcare professionals. This is due in part to gaps in both basic and applied research, often hindered by funding limitations and scientific skepticism.

Nevertheless, probiotics represent a promising frontier in medical and nutritional science. Continued research into their mechanisms and applications holds the potential to revolutionize our approach to preventive and therapeutic healthcare. The following are some of the well-established defined therapeutic probiotics belonging to several genera and species.

Part I: Members of Probiotics and Their General Physiological Functions

There are hundreds of probiotic strains across various genera and species, each possessing unique and scientifically validated therapeutic properties. These properties have significant applications in both **preventive** and **clinical medicine**.

Lactobacillus Species

- ***Lactobacillus acidophilus***: Alleviates lactose intolerance, chronic fatigue, IBS, depression, insomnia, high cholesterol, Candida overgrowth, and musculoskeletal pains. Notably boosts immune system activity.[6,7,8]
- ***Lactobacillus bulgaricus***: Helps with allergic rhinitis, viral colds, periodontal issues (including halitosis), eczema, leaky gut, cholesterol, triglycerides, and systemic inflammation.[9]
- ***Lactobacillus sporogenes*** (*Bacillus coagulans*): Effective against rotaviral, travelers, and antibiotic-associated diarrhea, IBS, IBD,

Helicobacter pylori infections, and respiratory tract infections. Enhances immune response and serves as an adjuvant to increase vaccine efficacy.[10]

- ***Lactobacillus rhamnosus***: Reduces gastrointestinal and viral infections by modulating the Th1/Th2 immune response. Offers broad-spectrum antimicrobial action and enhances vaccine-related immunity.[11]
- ***Lactobacillus plantarum***: Mitigates seasonal allergies, IBS, hypertension, anxiety, influenza (including H1N1 and coronaviruses), cancer risk, diabetes, and obesity. Strongly binds to intestinal epithelial cells, boosting immunity and resisting pathogenic colonization.[12]
- ***Lactobacillus casei***: Reduces viral infections, respiratory tract infections (including pneumonia), and rotavirus. Enhances immune response, particularly in the elderly, by countering immunosenescence.[13,14,15,16]
- ***Lactobacillus paracasei***: Exhibits potent immunomodulatory effects beneficial in IBD. Adheres well to intestinal epithelium and acts as an effective para-probiotic.
- ***Lactobacillus helveticus***: Reduces blood pressure, arthritis, anxiety, depression, and allergies. Supports bone health and resists gut dysbiosis due to its acid and bile tolerance.[17,18,19,20,21]
- ***Lactobacillus reuteri***: Reduces inflammatory diseases through suppressing production of pro-inflammatory cytokines, strengthens the intestinal barrier, also promoting T-Reg cell development and activity.

Bifidobacterium Species

- ***Bifidobacterium bifidum***: Treats IBS, constipation, *H. pylori* infections, ulcerative colitis, necrotizing enterocolitis, and lung infections.[22]
- ***Bifidobacterium longum***: Reduces inflammation, infection, and oxidative stress through immune system stimulation.[22]

Streptococcus and Enterococcus Species

- ***Streptococcus thermophilus***: Alleviates lactose intolerance, mucositis, gastritis, ulcerative colitis, and antibiotic-associated diarrhea. Enhances skin hydration and stimulates innate immunity (macrophages and natural killer cells).[15,22,23]
- ***Streptococcus faecium*** (*Enterococcus faecium*): Prevents infections by *Clostridium difficile*, *Listeria*, *Salmonella*, and *H. pylori* via broad-spectrum bacteriocin production. Promotes gut integrity and immune modulation through butyrate production and T-reg cell activation.[16]

Lactococcus Species

- ***Lactococcus lactis subsp. lactis***: Reduces allergies, bronchitis, alveolar inflammation, hypertension, LDL cholesterol, hearing loss, and viral infections. Stimulates dendritic and NK cells to enhance both innate and adaptive immunity.[16,24]
- ***Lactococcus lactis subsp. cremoris***: Mitigates depression, anxiety, and oxidative stress. Inhibits *Listeria monocytogenes* and boosts antioxidant production (e.g., folate, glutathione).[25]
- ***Lactococcus lactis subsp. lactis var. diacetylactis***: Strengthens immune response via cytokine and macrophage activation. Possesses antimicrobial and antifungal effects on gram negative pathogenic bacteria, as well as pathogenic yeast and molds.[16]

Other Beneficial Bacteria

- ***Leuconostoc mesenteroides subsp. cremoris***: Strong antimicrobial properties and excellent adhesion to intestinal epithelial cells. It significantly reduces gastrointestinal inflammation.
- ***Pediococcus acidilactici***: Treats diarrhea, constipation, and autoimmune conditions such as encephalomyelitis by inducing IL-10–producing regulatory T-cells.[26]
- ***Propionibacterium shermanii***: Balances intestinal microbiota, scavenges mycotoxins, inhibits pathogens, and fosters *Bifidobacterium* growth. Produces propionic acid with antifungal and antimutagenic effects.[27,28,29]
- ***Brevibacterium linens***: Stimulates immune response, enhances protein and fat digestion, lowers cholesterol, inactivates RNA viruses (e.g., coronaviruses), and reduces GI tumors.[30]

Yeasts and Molds

- ***Saccharomyces boulardii***: A probiotic yeast that improves mineral bioavailability, detoxifies mycotoxins, reduces inflammation and oxidative stress, and lowers risk for cardiovascular diseases, Alzheimer's disease, and cancer.[31]
- ***Penicillium camembertii***: A food-grade mold producing potent lipolytic and proteolytic enzymes. Supports digestion, gastrointestinal regeneration, and inflammation control.[31]
- ***Penicillium roquefortii***: A food grade mold, which produces Andrastatins A–D, with Andrastatin A showing strong anti-tumor effects and others acting as natural statins to inhibit cholesterol biosynthesis.[31]

Although it is basic, I would like to present microscopic images of the probiotics *Streptococcus thermophilus* and *Lactobacillus bulgaricus* to illustrate their morphological features, both in growth media and within the gastrointestinal (GI) tract. These probiotics, when in single-cell form, are more metabolically active than when in chains, due to their larger surface area, which enhances nutrient uptake and the discharge of metabolic end products. The details of which are presented in Fig. 1.

Figure 1: Microscopic picture of the mixed culture of probiotics, showing both the members of the genus *Streptococcus thermophilus* (shaped like o-o-o) and *Lactobacillus bulgaricus* (shaped like - - - -).

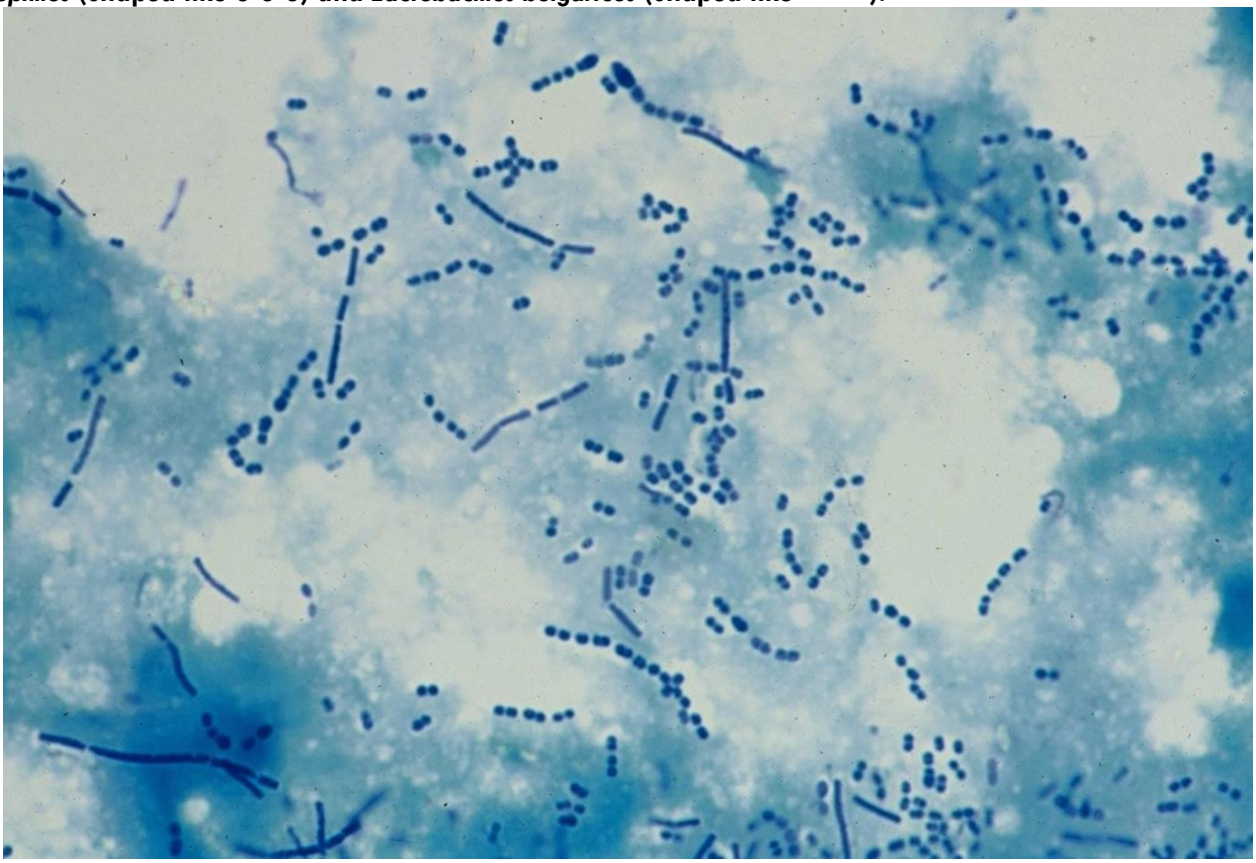
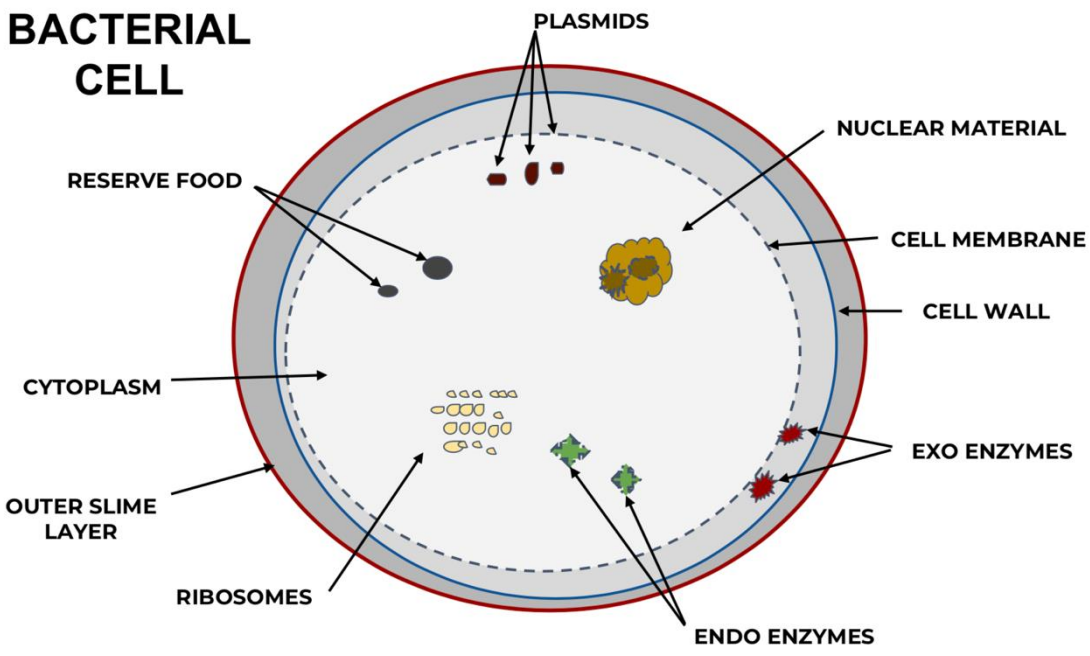


Figure 1 is reproduced from the following article of Dr. Malireddy S Reddy, published in the European Society of Medicine-Medical Research Archives (this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy MS (2024). Microbiological Techniques to Study Undue Strain Dominance Among Probiotic Bacteria in Order to Develop Compatible Multiple Mixed Probiotic Cultures to Prevent or Treat Diseases. Medical Research Archives. doi.org-10.18103/mra.v13i1.6201. (Reference No. 17)

Figure 2, a hand-drawn illustration, depicts various functional parts of a single *Streptococcus* probiotic cell. This diagram highlights the locations of extra-chromosomal genes (plasmids), nuclear material within the cytoplasm, ribosomes, and the cellular membranes.

Figure 2: Morphology of single *Streptococcus* probiotic cell.



It is important to note that the plasmids are synthesized by the probiotic bacteria themselves to encode specific enzymes necessary for their survival. These plasmid-encoded enzymes not only offer survival advantages to the bacteria but are also responsible for the therapeutic effects of probiotics. In pathogenic bacteria, similar plasmids may be responsible for multiple antibiotic resistance.

Figure 3 illustrates the human intestinal tract, showing the approximate distribution of microbiota from the stomach to the distal end of the large intestine. This allows one to appreciate the abundance and localization of microorganisms within the GI tract, which perform a range of functions including digestion and immune support.

Figure 3 clearly points out that the distribution and numbers of microbiota largely depends on the pH (pH 2 in the stomach) and the alkaline inhibitory secretions such as bile, etc. Although the human mouth has significant numbers of bacteria per gram, such bacterial numbers get reduced to the tune of perhaps 100 per gram in the stomach due to low pH acids. Subsequently the bacterial numbers start to increase in various segments of the small intestinal tract - with the majority being in the colon - to carry on the specific functions at various locations of the gastrointestinal tract. The total number of microorganisms in the human GI tract are roughly 100 trillion, represented by over 1,000 genera and species.

Figure 3: Approximate concentration of microflora in various sites of the Gastrointestinal (GI) tract.

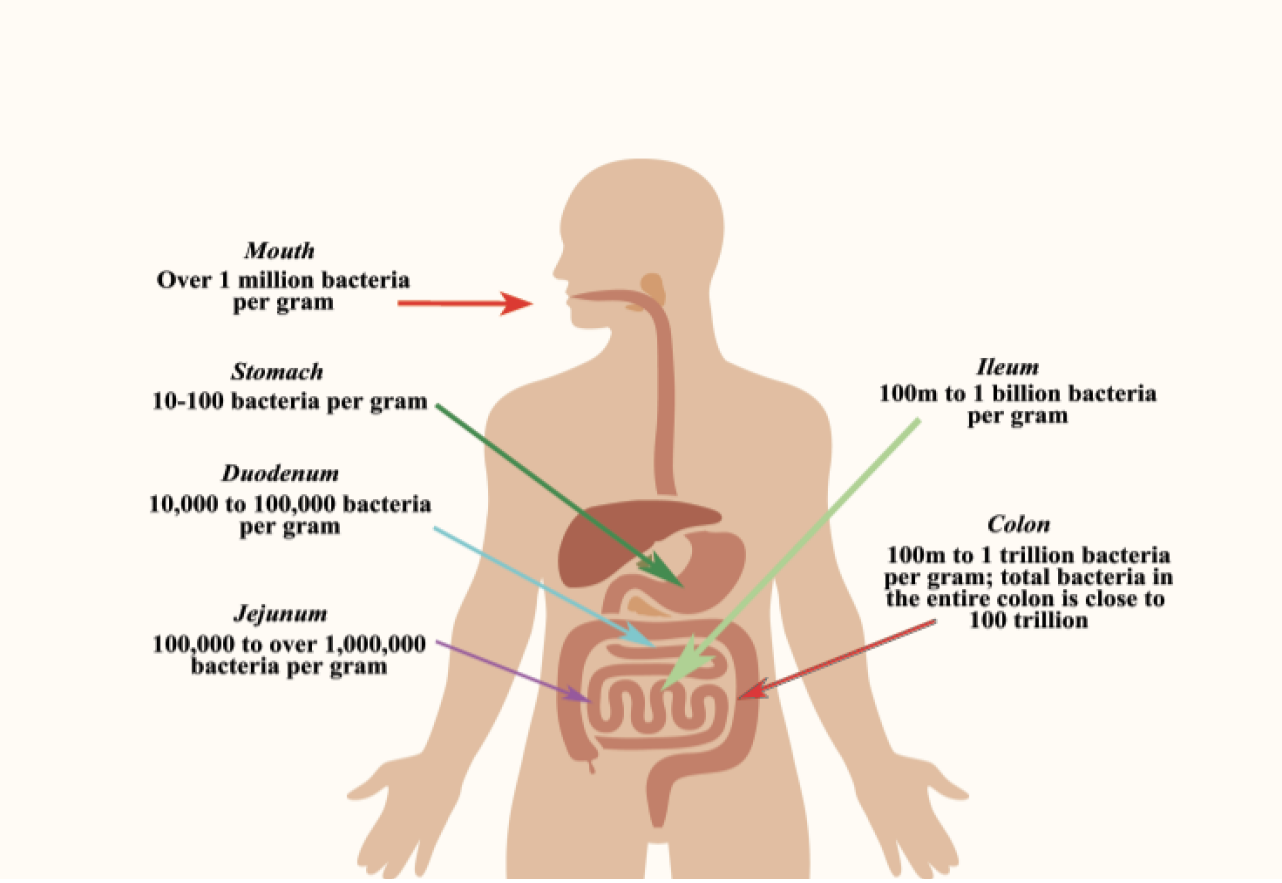
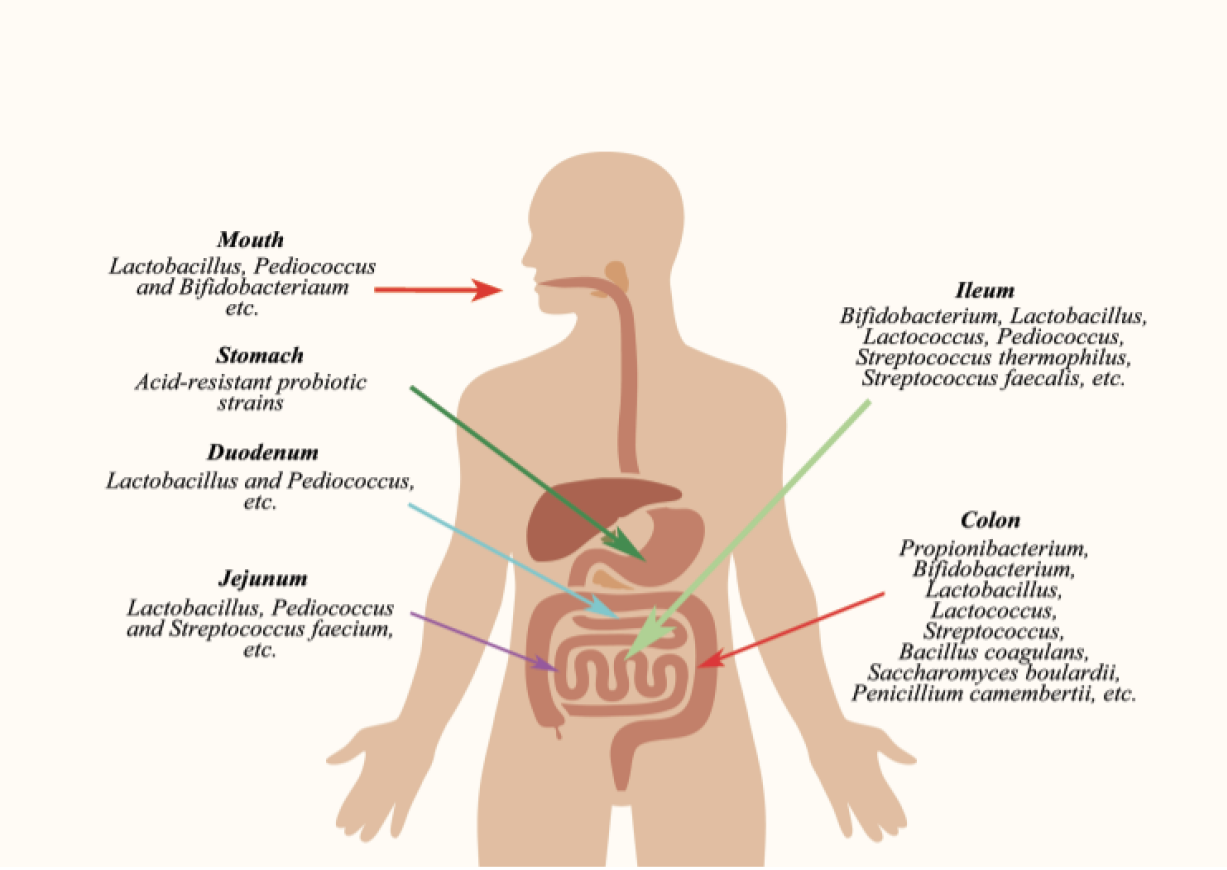


Figure 4 presents the approximate distribution, location, and adhesion sites of specific probiotics in the human GI tract. The total number of microorganisms in the GI tract is estimated to be around 100 trillion, of which approximately 20%—or 20 trillion—are probiotics.

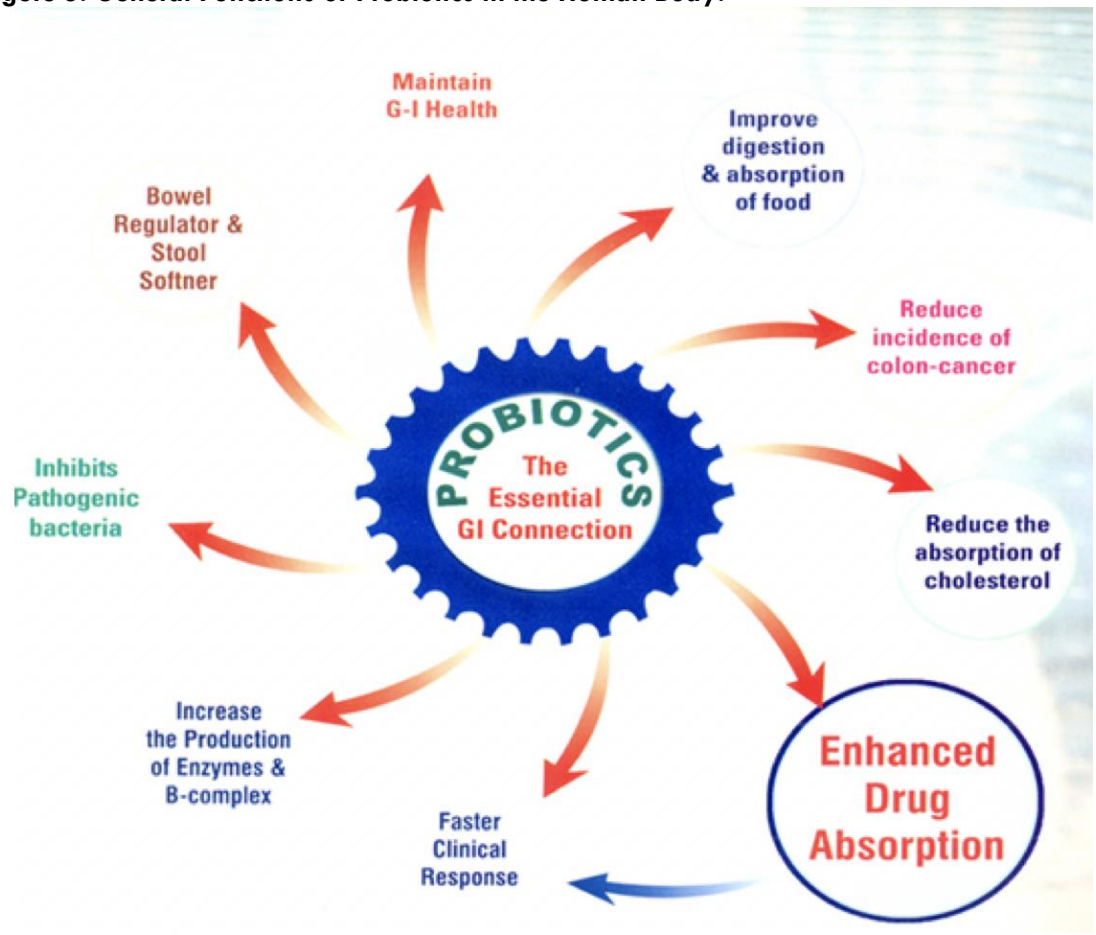
Figure 4: General distribution of Various Genera and Species of Probiotics in the Gastro Intestinal (GI) tract.



It is distinctly clear from Figure 4 that most of the major functional probiotic bacteria are located in the ileum and colon. Overall, species belonging to the genus *Lactobacillus* and *Pediococcus* are located throughout the GI tract, starting from the duodenum to the distal end of the colon. The species belonging to genus *Lactobacillus, Bifidobacterium* and *Streptococcus* are mostly located in the jejunum and ileum, where they exhibit their maximum therapeutic effects. It is worthwhile to note that species belonging to the genus *Propionibacterium* and beneficial yeast and molds are also located in the colon. The total number of probiotics in the GI tract are roughly 20 trillion out of 100 trillion microorganisms constituting the Microbiota and Microbiome.

Figure 5 is a simplified illustration summarizing the major functions of probiotics in the human body. Since the primary focus of this article is to highlight the role of probiotics in preventive and clinical health, it is worthwhile to include these fundamental aspects of their morphology and distribution in the GI tract—particularly for readers with minimal background in microbiology.

Figure 5: General Functions of Probiotics in the Human Body.



The significant general functions of probiotics in the GI tract are digestion, reduction of cholesterol absorption, production of vitamins and beneficial enzymes. In addition, they facilitate the absorption of therapeutic drugs (specifically herbal and nutraceuticals) by eliminating destruction by other saprophytic organisms in the distal end of the GI tract. General functions of probiotics also include facilitating the absorption of minerals by maintaining a proper pH.

Finally, Table 1 in Part II of this article lists various therapeutic functions of probiotics. The pathophysiology of a specific disease(s)and physiological molecular mechanism of probiotic therapeutic action are described under several specific headings in a chronological order.

Part II: Specific Proven Therapeutic Functions of Probiotics to Prevent/ Treatment of Various Diseases

The specific proven therapeutic functions of probiotics are summarized in Table 1 below, after which we will expand upon each property in greater detail.

Table 1: Specific Proven Therapeutic Functions of Probiotics.

Therapeutic Functions
1. Immunomodulation[32]
2. Reduction of Intestinal Infections[33]
3. Reduction of Lactose Intolerance[34]
4. Suppression of Helicobacter Pylori[35]
5. Control of Cytokine Storm and Covid-19
6. Control of Diabetes
7. Control of Hypertension[33]
8. Control of Obesity[32,35]
9. Prevention and Control of Allergies[32]
10. Improving anti-aging and Longevity
11. Prevention/Treatment of Hospital Acquired Infections
12. Prevention or Suppression of Cancer
13. Prevention of Various Diseases Through Probiotic Selection

1) IMMUNOMODULATION (BY PROBIOTICS)

This is a critical and essential function induced by probiotics. The immune-stimulating activity is primarily attributed to their bacterial cell envelope constituents, such as peptidoglycan. Various studies indicate that probiotics stimulate the production of antibodies, enhance systemic macrophage activity, increase interferon levels, and elevate the number of natural killer cells. To influence the immune system effectively, probiotics must activate the lymphoid cells of the gut-associated lymphoid tissue (GALT), which are diffusely distributed among the epithelial cells and populate the lamina propria and submucosa.

The immunogenic properties of probiotic bacteria, such as *Propionibacterium*, do not reside in extracellular slime. Rather, their cell walls possess antigenic properties, further supporting the idea that the immunomodulatory effect of probiotics is a function of their cell wall composition—which can vary between strains. It is also noteworthy that even dead probiotic cells can exert immunomodulatory effects to some extent due to their retained cell wall components. Thus, probiotics exert superior immunomodulation through the production of their immunomodulins. Immunomodulation by probiotics is an essential requisite for human survival.

2) REDUCTION OF INTESTINAL INFECTIONS

These infections are commonly caused by pathogenic bacteria. Under normal circumstances, such pathogens are suppressed by the beneficial microflora of the gastrointestinal (GI) tract. A key component of this beneficial flora is probiotics, which have the innate ability to outcompete harmful bacteria.

Probiotic therapy has been shown to control antibiotic-induced diarrhea effectively. *Lactobacillus* and *Bifidobacterium* species have been used successfully in both children and adults to treat intestinal infections. Probiotics act via multiple mechanisms: competition for nutrients, secretion of antimicrobial substances, lowering of intestinal pH via short-chain fatty acid production, blocking of pathogen adhesion and toxin receptor sites, immune stimulation, and attenuation of bacterial and viral virulence.

In this connection, it is worthwhile to mention regarding the probiotic-produced bacteriocins and their role in inhibiting pathogenic bacteria involved in several infections. The bacteriocins are ribosomal synthesized antimicrobial peptides produced and excreted by probiotics. These bacteriocins exhibit a wide range of inhibitory effects on several pathogens. However, unlike antibiotics, they are non-toxic and non-allergenic and can be ultimately inactivated in the gastrointestinal (GI) tract after they exert their functions. Unlike antibiotics, pathogenic bacteria cannot develop resistance to bacteriocins. The specific bacteriocins produced by several strains of probiotics are listed in **Table 6** towards the end of this publication. Selecting proper probiotic strains which are intended to be used as therapeutic agents to cure a specific disease must be based on the bacteriocins they produce.

3) REDUCTION OF LACTOSE INTOLERANCE

Lactose is a disaccharide composed of glucose and galactose. It is hydrolyzed by the enzyme lactase (or β-galactosidase), which is produced by the epithelial cells of the ileum. In some individuals, lactase is absent or produced in insufficient quantities. Consequently, undigested lactose causes gastrointestinal symptoms such as bloating, gas, and diarrhea—collectively known as lactose intolerance. It affects nearly half of the global population.

Probiotic organisms, especially lactic acid-producing bacteria, can help by producing lactase. This lactase is often encoded by extrachromosomal plasmids in the bacteria. When these probiotics colonize the ileum, they can compensate for the host's lactase deficiency, thereby alleviating symptoms. Lactose intolerance is particularly prevalent in the elderly due to reduced endogenous lactase production. Therefore, multiple mixed-strain probiotics should be administered routinely to older adults. Additionally, it has been observed that probiotic levels naturally decline with age due to physiological factors. Deficiency of lactase enzyme is one of the prime reasons for the impaired absorption of calcium in the ilium due to the impairment of maintaining a proper pH. Derangement of calcium absorption leads to osteopenia and osteoporosis, in addition to hypertension. Thus, it is vital to maintain proper probiotics in the GI tract.

4) SUPPRESSION OF *HELICOBACTER PYLORI*

H. pylori is a gram-negative, spiral-shaped bacterium that colonizes the stomach lining by creating microcolonies generating high ammonia production from urea (via urease enzyme). It is a well-established cause of chronic gastritis, peptic ulcers, gastric atrophy, and gastric cancer.

In 1994, the International Agency for Research on Cancer classified H. pylori as a Group 1 carcinogen, the definitive cause of gastric cancer. Some probiotic strains can suppress or inactivate *H. pylori*. The likely mechanisms include the production of bacteriocins, antimicrobial peptides, and other inhibitory substances. It is an excellent and desirable practice to administer probiotics as a part of a preventative therapy to reduce the incidences of *H.pylori* infection.

5) CONTROL OF CYTOKINE STORMS AND COVID-19 (BY PROBIOTICS)

A cytokine storm is a dangerous, systemic inflammatory response characterized by the over-activation of immune cells and excessively high levels of circulating cytokines.[36,37] This uncontrolled immune reaction can damage healthy tissues and contribute to various severe conditions, including autoimmune diseases and complications from infections like COVID-19.

Cytokines ("cyto" means cells and "kinos" means moving) are crucial cell-signaling molecules, acting as messengers within the immune system.[38,39] They are categorized into:

- **Pro-inflammatory cytokines** (e.g., IL-1, IL-6, IL-8, IL-12, IL-18, TNF-alpha, GM-CSF, IFN-gamma): These are produced mainly by T-

Helper cells (TH) and Macrophages. They promote, upregulate and amplify inflammatory responses. IL-6 is a particularly significant pro-inflammatory cytokine.

- **Anti-inflammatory cytokines** (e.g., IL-4, IL-10, IL-11, IL-13, TGF-beta): These work to suppress inflammation and restore immune balance. IL-10 is a key anti-inflammatory cytokine.
- **Regulatory cytokines** (e.g., IL-21, IL-35, and dual roles by TGF-beta and IL-10): These orchestrate a balanced and optimal immune system response.

5.1: Related Immunology Terminologies used in Cytokine Storm

Interferon vs. Interleukin

An **Interferon** is denoted as IFN. These Interferons are mainly involved in inhibiting viruses by making the neighboring cells non-permeable to such infections. The examples of Interferons are IFN-alpha and IFN-gamma etc.[40]

An **Interleukin** is denoted by IL. The meaning of Interleukin is "inter" means between and "Leukin" means Leucocytes or White Blood Cells. The examples of Interleukins are IL-6, IL-10 etc. They serve as Messenger molecules between several immune cells.[41]

Chemokines

The term "Chemo" means "chemical "and "Kinos" means moving. Chemokines also come under Cytokines. The cytokines are the general category of Messenger molecules, whereas Chemokines are special Cytokines involved in the migration of White Blood Cells to the infected or damaged tissues.[42,43] The inflammatory Chemokines include: CCL2, CCL3, CXCL1, CXCL2, CXCL8, and CXCL10, and they are produced in Lymphoid tissue and Thymus. Thus, the general term Cytokines include Chemokines, Interferons, and Interleukins etc.

In a nutshell, when the body encounters a pathogen, the innate immune system (e.g., neutrophils, macrophages) triggers the production of cytokines, which then activate the adaptive immune system (T-cells, B-cells) to produce more cytokines. While typically functioning at very low concentrations (Pico molar), during severe infections or inflammation, cytokine levels can surge dramatically (nano and micro molar), leading to a cytokine storm leading to death and decay. The only T-cells capable of dampening this storm are **T-regulatory (T-reg) cells**, which suppress pro-inflammatory cytokine production and enhance anti-inflammatory and regulatory cytokines.

5.2: What kind of Diseases or Syndromes in which the Cytokine Storm Plays a Crucial Etiological Role?

They are as follows:

Sepsis; Hemophagocytic Lymph histiocytosis (HLH); Macrophage Activation Syndrome (MAS); Graft-Virus Host Disease (GVHD); Immunotherapy -Induced Cytokine release Syndrome (CRS); Dengue Fever; Viral Hemorrhagic Fever; Influenza Virus Infection; Auto immune diseases include Rheumatoid Arthritis, and Lupus etc.; Acute Respiratory Distress Syndrome (ARDS); Covid-19 infection due to SARS-CoV-2 Corona Virus etc.

Most of the aforementioned diseases are as a result of the immune system mistakenly attacking healthy tissues triggering the cytokine storm, which will ultimately induce severe symptoms and cause multi organ failures.

Out of all the diseases outlined above, I would like to focus on the Pathophysiology of the recent Pandemic created Covid-19 infection, which induced ARDS due to severe Cytokine storm, and also attempt to explain the physiology behind the preventative and curative aspect of these syndromes with the use of probiotics and their immunomodulins.

5.3: Specific Details of Cytokine Storm during Covid-19 infection

Induction of cytokine storm, due to Covid-19 disease causing SARS-CoV-2 corona virus starts initially with the reaction of innate immune cells to inactivate the virus. At the same time, the innate immune cells produce cytokines to activate the adaptive immune system. The corona viral antigens attached to MHC-2 (major histocompatibility complex-2) on the antigen presenting cells, activate CD 4 +T cells and they in turn activate TH-17 cells. The activated TH-17 in turn recruits and sends more Neutrophiles and Macrophages (innate immune cells) to the infection site with the aid of Interleukins and chemokines. In addition, CD-4 + T cells also produce abnormal number of T-killer cells to attack the SARS-CoV-2 virus present in the lung tissue, leading to more damage to the lung. Thus, the combination of excess Neutrophile infiltration and leakage of plasma from blood vessels results in the preliminary stages of ARDS (acute respiratory distress syndrome). Meanwhile CD-8+ T cells, after recognizing SARS-CoV-2 viral peptides in the infected lung tissue, releases excess number of cytotoxic molecules to stop further spread of the virus. Adding insult to the wound, the corona virus also selectively induces Macrophages to produce inflammation provoking IL-6, which in turn regulates the PD-1 and CTL-4 immune check point receptors on T-cells with the aid of the virus infected cell induced ligands to make the T-cells infective. This is one-way viruses act to protect themselves from the immune system. This will cause severe decrease in lymphocyte count from 3000 per microliter to roughly 1000, resulting in lymphocytopenia. Thus, cytokine storm results in causing T- lymphocyte exhaustion and severe lung tissue damage, ultimately end up with severity of disease -Covid-19 with resulting ARDS and death. The exact mechanisms of how the corona virus propagates in the infected Eukaryotic cells, and how the corona virus induced host cell ligands inactivate T-cells to induce lymphocytopenia during Covid-19 corona viral infection is presented in Fig. 6 and Fig. 7.

FIGURE 6: Pictorial Presentation of SARS-CoV-2 Viral Infection.

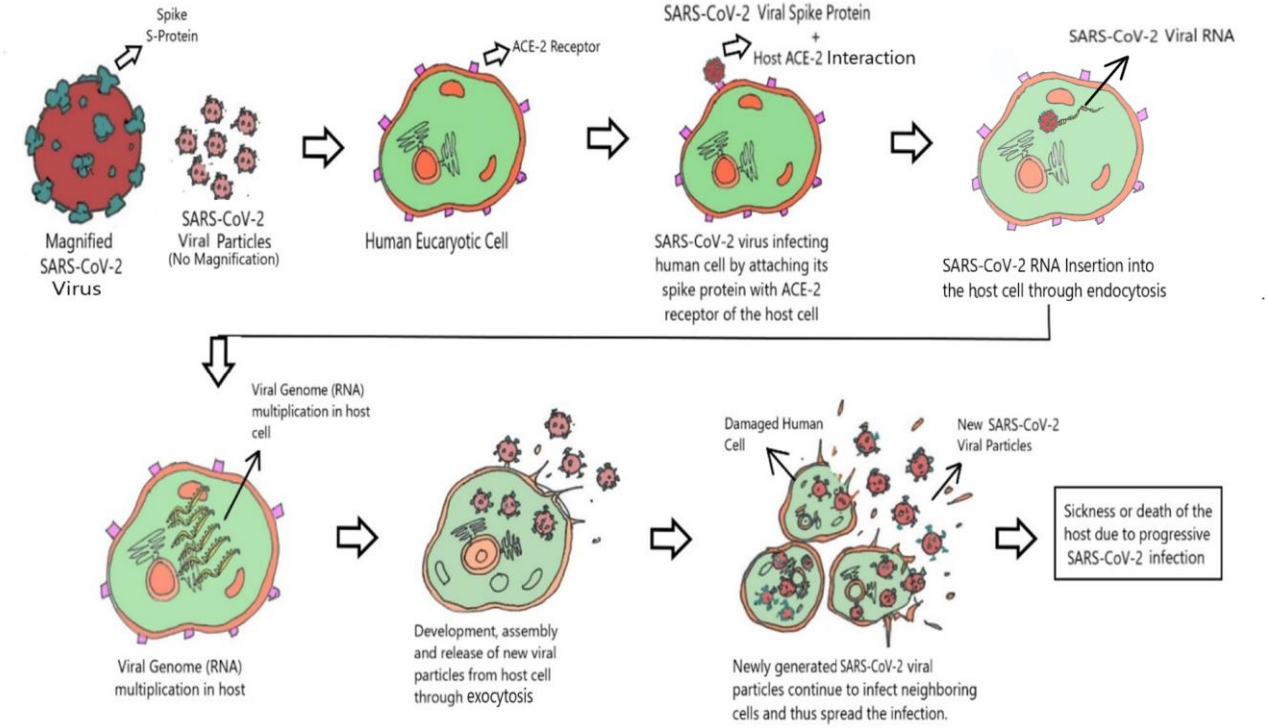
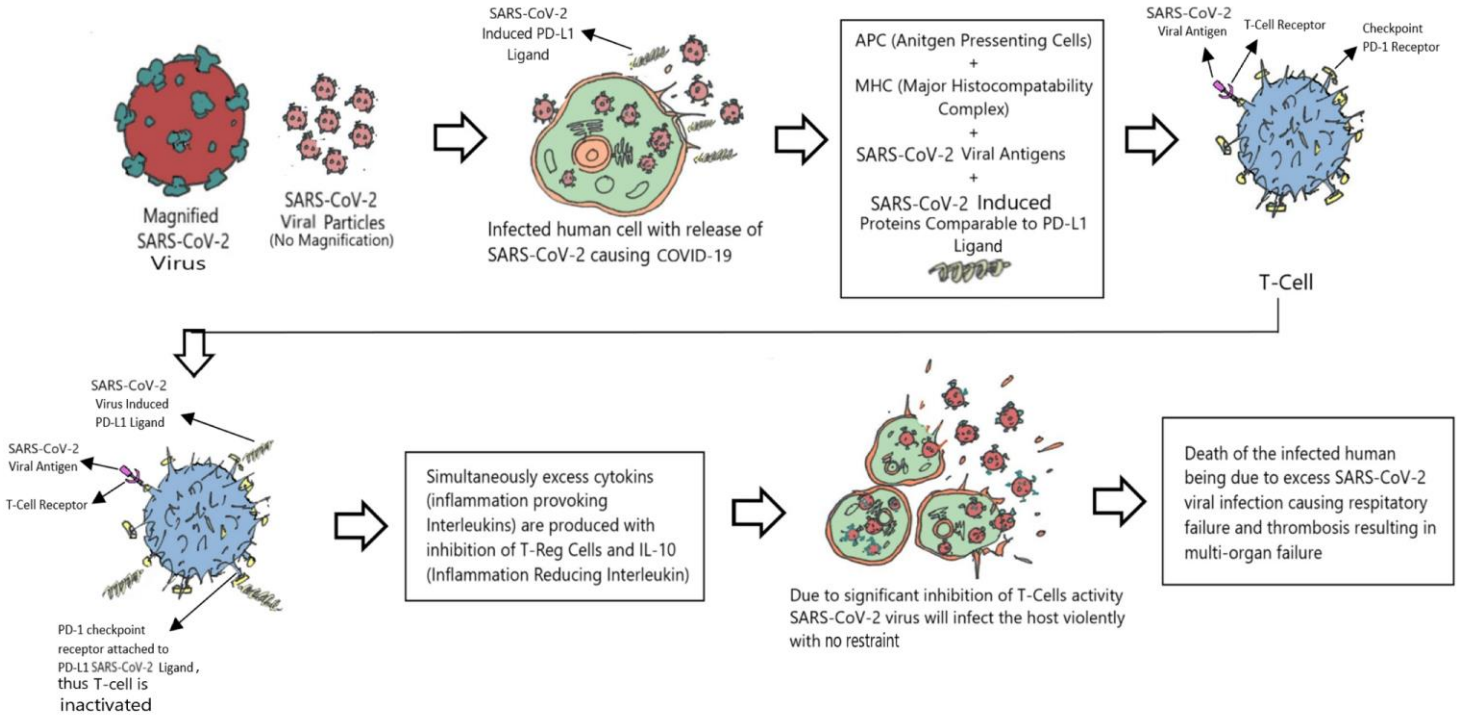


FIGURE 7: Pictorial Presentation of the COVID-19 Disease Pathogenesis through Dysfunction of T-Cells due to Interaction of SARS-CoV-2 Induced PD-L1 Ligands with PD-1 Immune Checkpoint Receptors on T-Cells.



5.4: Covid-19 Disease Progression

The infective pattern and multiplication of SARS-CoV-2 virus in Eukaryotic cell is presented in Fig-1. The corona virus spike attaches to the ACE-2 receptor site on the eukaryotic cell and thus releases the single stranded positive sense RNA molecule. The viral RNA starts multiplying, making several progenies. The fully formed virions are released through exocytosis out of the infected cell and continue the infection at a rapid pace. Since SARS-CoV-2 virus has roughly 90 spikes, the chances of the viral spike attachment to host cell ACE-2 receptor is significantly greater and after attachment viral RNA is integrated into the host cell. It takes roughly 15 minutes from the time it attaches to the cell and inject viral RNA into the host eukaryotic cell. From the time the viral RNA is injected into the eukaryotic cell to the time the release and appearance of the newly made virion is called the eclipse period. Generally, the eclipse period in corona virus is roughly 12-36 hours. The number of viral particles released from each viral infected cell is called burst size. It has been reported that the burst size of the corona virus is roughly 700 virions from each infected cell. The

molecular details of the infection pattern are outlined in depth in the publication of Reddy.[44]

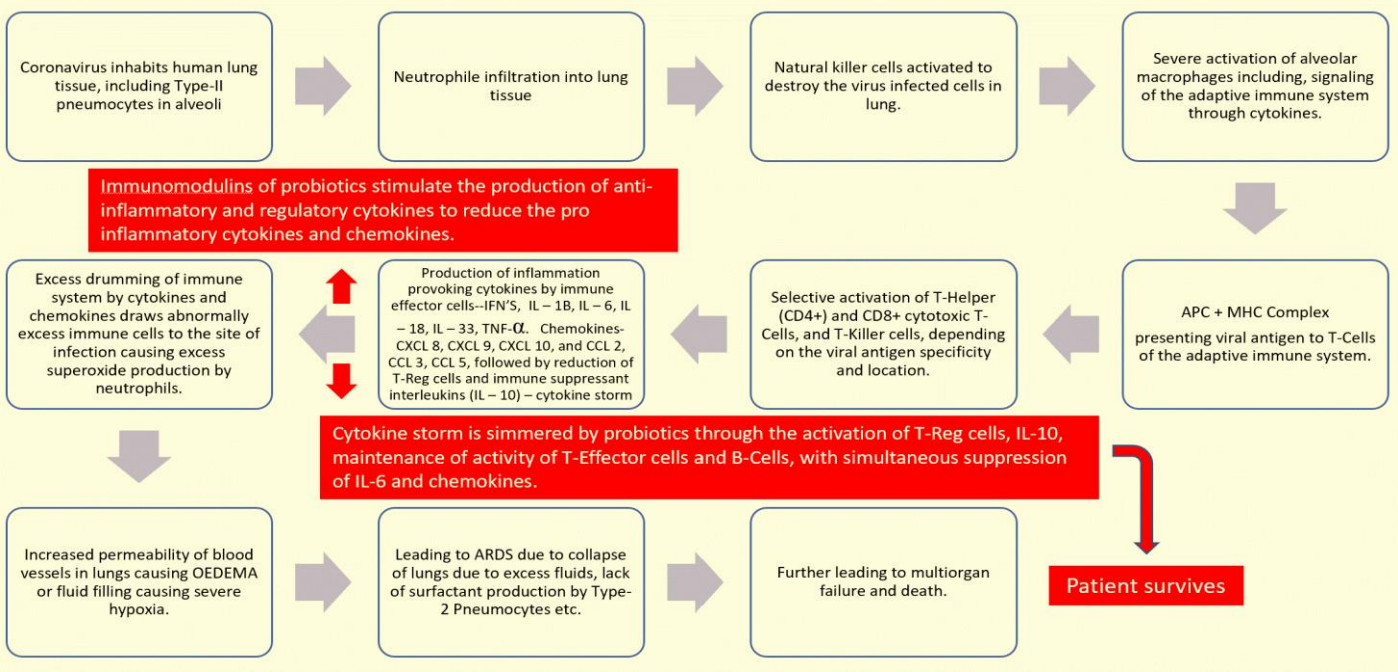
5.5: Role of probiotics along with their immunomodulins for preventing or treating Covid-19 infection due to SARS-CoV-2 virus through immunomodulation, and the prevention of Lymphocytopenia

Probiotics, along with their **immunomodulins** (substances produced by probiotics that influence the immune system), are believed to mitigate cytokine storms through a sophisticated process of immunomodulation. Essentially, they aim to restore the delicate balance of the immune system by:

1. **Up-regulating beneficial immune responses:** Probiotics can increase the production of **anti-inflammatory cytokines** (like IL-10) and **regulatory cytokines**. They also promote the activity and proliferation of **T-regulatory cells**, which are essential for reining in excessive inflammation. Furthermore, they can enhance the function of T-effector cells and B-cells, ensuring an effective, but controlled, immune response.
2. **Down-regulating harmful immune responses:** Concurrently, probiotics work to reduce the production of **pro-inflammatory cytokines** (such as IL-6) and **chemokines** (specialized cytokines that direct immune cells to sites of infection), thereby suppressing the uncontrolled inflammatory cascade characteristic of a cytokine storm.

This entire mechanism of cytokine storm control by probiotics is presented in Fig 8.

FIGURE 8: Schematic presentation showing the COVID-19 induced cytokine storm, and its control with the aid of multiple mixed strain probiotics and their immunomodulins.

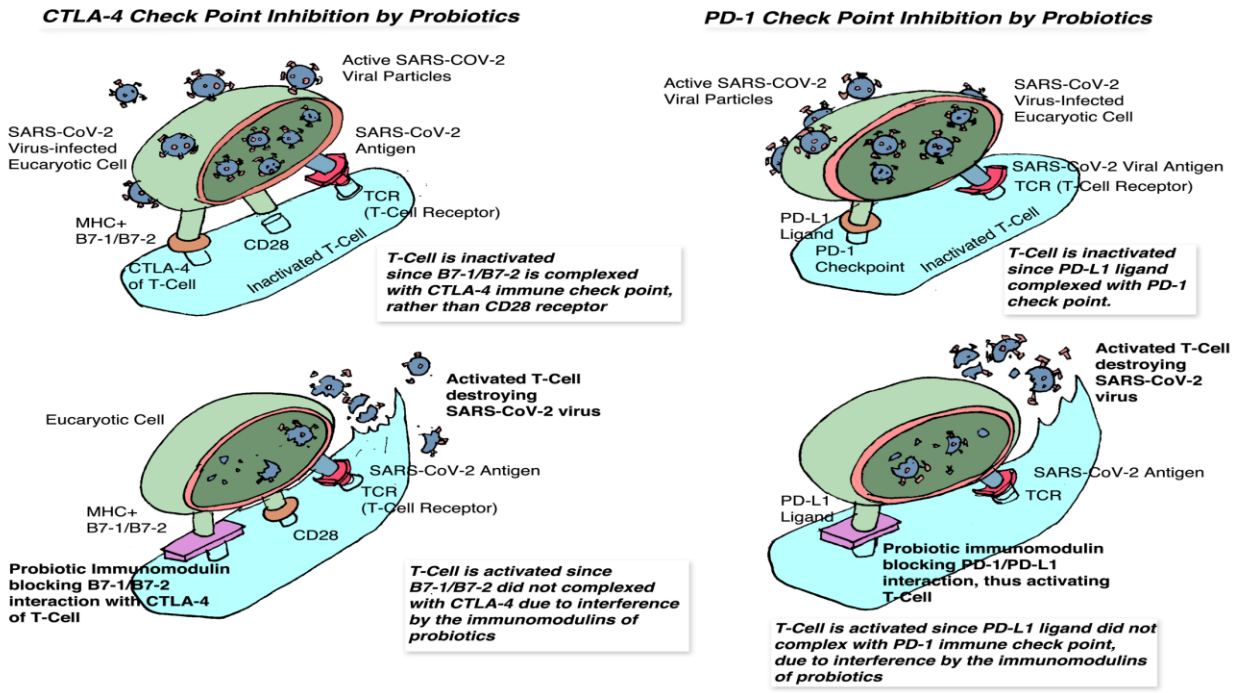


5.6: The Role of Probiotics to reduce Lymphocytopenia in COVID-19

In conditions like severe COVID-19, the SARS-CoV-2 virus can cause a significant decrease in lymphocyte count (**lymphocytopenia**), leading to T-cell exhaustion and compromised immune function. This occurs partly because the virus can inactivate T-cells by interacting with their **immune checkpoints** (like PD-1 and CTLA-4 receptors). These checkpoints normally act as "brakes" on T-cell activation, preventing the immune system from attacking the body's own tissues. However, in viral infections, ligands produced by infected cells (PDL-1 and B7-1/B7-2) can bind to these check points (PD-1 and CTLA-4) on T-cells, effectively deactivating them and allowing the virus to multiply unchecked.[45,46,47]

Multiple mixed-strain probiotics and their immunomodulins may act as **checkpoint inhibitors** themselves, much like therapeutic antibodies. By occupying or modulating these immune checkpoints on T-cells, probiotics could prevent the virus-induced ligands from attaching and inactivating the T-cells. This would help preserve T-cell function, prevent their exhaustion, and support the host's ability to mount an effective immune response against the virus, thereby mitigating lymphocytopenia and the severity of the disease. The details on how probiotics can act as check point inhibitors is presented in Fig. 9.

FIGURE 9: Pictorial presentation showing immunomodulins of probiotics acting as checkpoint inhibitors to block CTLA-4 and PD-1 immune checkpoints on T-Cells from interacting with B7-1 / B7-2, and PD-L1 Ligands, thus activating T-Cells to inhibit the SAR-CoV-2 Virus.



Figures 6,7,8 and 9 are reproduced from the following article of Dr. Malireddy S Reddy published in the JAAPI Journal (this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy MS. Mechanism of cytokine storm in COVID-19: how can probiotics combat it? JAAPI. 2021;1(3):27-35.

In essence, probiotics contribute to orchestrating an optimal immune system response, aiming to prevent the hyperactivation seen in cytokine storms and, by extension, reduce the risk or severity of associated conditions, including certain autoimmune diseases and severity of progression of viral infections.[44]

6) CONTROL OF DIABETES (BY PROBIOTICS)

There are two types of Diabetes Mellitus: **Type 1 Diabetes (T1DM)** and **Type 2 Diabetes (T2DM)**.
By definition, Diabetes Mellitus is a **chronic metabolic disorder** resulting from either the body's inability to produce enough insulin or its inability to effectively use the insulin it produces, leading to elevated blood sugar levels. As of mid-2025, approximately 537 million adults globally are living with diabetes, a number projected to rise to 783 million by 2045. This disorder is characterized by **blood glucose dysregulation**.[48,49,50]

The beta cells of the Islets of Langerhans in the pancreas produce hormone insulin, which controls the entry of blood glucose into eukaryotic cells to generate ATP through the glycolytic cycle. In T1DM, the pancreas produces little or no insulin, leading to high blood sugar levels. In contrast, in T2DM, the pancreas may produce insufficient insulin, or even a normal level of insulin, which may not effectively facilitate glucose uptake into cells due to insulin resistance, resulting in excess glucose in the blood (**hyperglycemia**).[51]

According to the literature, **90% of diabetic cases are T2DM**, with roughly 10% being T1DM. T2DM is currently a global pandemic. The **WHO (World Health Organization)** defines it as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism, resulting from defects in insulin secretion, insulin action, or both. It has been identified as a leading cause of blindness, end-stage renal disease, lower limb amputation, and cardiovascular disease. Although diabetes was first reported in Egypt over 3,000 years ago, the distinction between T1DM and T2DM was established only in 1936.[52-61]

6.1: Etiology and Pathophysiology of Type 2 Diabetes

T2DM is largely caused by impaired insulin production and secretion by pancreatic beta cells, as well as peripheral tissue **insulin resistance.** Before I go into how probiotics can reduce hyperglycemia, a brief description of the genesis of hyperglycemia is presented.
The following etiological factors have been attributed to the onset of T2DM:

- **Obesity:** Generally considered a primary factor, as obese individuals have a 90% chance of developing T2DM, due to insulin resistance.
- **Stress and Depression:** These increase the risk of T2DM.
- **Environmental Factors:** Pollution and excessive use of food preservatives have also been implicated.
- **Pathogenic Viruses:** Viruses such as Herpes Simplex and Hepatitis C have been attributed as causative factors. Specifically, a liver infected with Hepatitis C virus promotes severe insulin resistance.

Out of all several etiological factors, I would like to discuss the role of Obesity and insulin resistance in the onset of T2DM.

Diabetic onset is partly due to obesity, which induces **peripheral insulin resistance**. Obesity is characterized by elevated levels of cytokines and fatty acids. Initially, the onset of insulin resistance increases the demand for insulin production by the beta cells of the Islets of Langerhans in the pancreas, achieved through increasing the volume of cells. Under chronic insulin resistance, beta cells eventually cannot cope with the demand for insulin production, thus significantly slowing down production and undergoing **apoptosis**. This results in hyperglycemia.

In addition, low insulin levels also alter **normolipidemic** states (normal triglycerides, HDL, LDL, and cholesterol in the blood). Higher levels of these lipids due to decreased insulin levels can lead to cardiovascular complications. Another indication of T2DM is an increase in **proinsulin levels** in the blood. Proinsulin is the inactive precursor to insulin produced in the pancreas. It is a single-chain protein that converts into insulin and C-peptide (connecting peptide) through the removal of C-peptide by prohormone convertase enzymes. Normally, small amounts of proinsulin enter the blood along with insulin, typically higher after meals and in individuals with insulin resistance or early stages of T2DM. In healthy individuals, proinsulin in the blood can be roughly 20% of total insulin; however, in T2DM, it can reach up to 50%, indicating beta cell dysfunction. The lack of conversion of proinsulin into insulin deficiency leading to T2DM.

6.2: Insulin Resistance (IR)

The term **insulin resistance (IR)** refers to why glucose levels remain elevated even when there is no insulin deficiency. Normally, blood glucose is reduced by cellular uptake using **GLUT transporters**. Some cells have transporters that are responsive to insulin (e.g., **GLUT4** in muscle and adipose cells), while others have transporters that do not require insulin for activation (e.g., glucose-dependent cells including red blood cells, white blood cells, renal papilla cells, nervous system cells, cardiac muscle cells, etc.). Some muscle cells possess both non-insulin responsive and insulin-responsive (GLUT4) transporters. As ironic as it sounds, it has been attributed that **Hyperinsulinemia**, due to excess production and more concentration in the blood, is one of the causes of insulin resistance in T2DM.[84-88]

According to available literature, although the etiology of diabetes is multifactorial, certain facts have been established. T1DM is primarily due to the total destruction of pancreatic beta cells, largely due to autoimmune reactions and genetic factors. In contrast, T2DM is attributed to reduced insulin production due to partial cessation of pancreatic beta cell function, often linked to obesity-related insulin resistance, resulting in hyperglycemia and hyperinsulinemia. Additionally, inflammation, pathogenic viral infections, and depression have been listed as etiological factors for the genesis of T2DM.

6.3: Mechanism by which Probiotics Reduce Blood Sugar Levels to Prevent or Treat T2DM

Probiotics and their immunomodulins have a significant effect, both directly and indirectly, on the prevention, control, and/or treatment of diabetes. This can be explained logically using the following available experimental evidence in relation to Inflammation reduction, reduction of viral infections, controlling depression and stress, and regulation of fat metabolism by probiotics.[62-83]

6.4: Inflammation Reduction

As discussed in relation to reducing COVID-19 infection, a similar physiological mechanism applies to reducing inflammation in T2DM. The primary culprit in inflammation is predominantly the **cytokine storm**, due to an overactive immune system, characterized by elevated pro-inflammatory cytokines such as IL-6 and TNF-alpha. This cytokine storm, often related to obesity, ultimately leads to the slowing of beta cell functions, which are already overburdened due to increased demand for insulin production. Such cytokine storm and related chain reactions increases the accumulation of misfolded proteins in the endoplasmic reticulum (ER), leading to **ER stress**. Oxidative stress and ER stress can cause apoptotic cell death, leading to the progressive failure of even residual beta cells in the pancreas. This reduced insulin level leads to hyperglycemia, which further damages beta cells due to glucose toxicity. Additionally, hyperglycemia demands more insulin production, resulting in hyperinsulinemia, which can also contribute to beta cell damage.

Probiotics and their immunomodulins, through the activation of anti-inflammatory cytokines such as IL-10 and TGF-beta, can **simmer inflammation**. Simultaneously, probiotics also reduce the production and activity of pro-inflammatory cytokines to protect beta cells from deterioration.

It has also been hypothesized that our own T-cells can exhibit autoimmunity, destroying beta cells by misreading self-antigens as foreign proteins. Probiotics possess the innate ability to maintain and control **immune checkpoints**, which serve as negative regulators of T-cells, preventing them from attacking beta cells in the Islets of Langerhans. Furthermore, probiotics have the intrinsic ability to activate **T-regulatory cells**, which can significantly mitigate abnormal T-cell activity encountered in a cytokine storm. Thus, peripheral insulin resistance can be brought under control by restoring the function and repair of beta cells with the aid of probiotics and their immunomodulins.

6.5: Reduction of Pathogenic Viral Infections

Viral infections, such as herpes and hepatitis C, have been attributed as causative factors that increase insulin resistance, leading to T2DM. Probiotics have a significant effect on reducing viral infections by activating the immune system through immunomodulation. A detailed description of how probiotics can inhibit viral multiplication through immunomodulation was presented earlier.

6.6: Reduction of Depression and Stress

Depression and stress have also been identified as causative factors for T2DM. These can be brought under control by probiotics. This is accomplished by maintaining the cell wall integrity of the intestinal epithelial cells by probiotics and their immunomodulins, allowing **tryptophan** to be absorbed to generate **serotonin**, which acts as a nerve stimulant to prevent or suppress depression.

It has been reported that stress can alter the composition of intestinal microbiota, resulting in **dysbiosis**, which ultimately negatively influences the immune system and the health of human cells and tissues, including pancreatic beta cells. Probiotics and their immunomodulins can override the stress effect on the immune system by restoring the composition of microbiota and microbiome.

6.7: Regulating Fat Metabolism

Finally, the disturbance in fat metabolism due to T2DM, characterized by an increase in blood triglycerides, LDL, and total cholesterol, can be brought under control through the proven benefits of probiotics in reducing triglycerides and hypercholesterolemia. Probiotics can correct hypercholesterolemia by adsorbing cholesterol, through hydrolyzing the bile salts and thus, eliminating the cholesterol in feces, and also by assimilating the dietary cholesterol in the gastrointestinal tract.

6.8: Practical Illustration

As a practical illustration, a controlled experiment during the COVID-19 pandemic demonstrated that probiotics, along with their immunomodulins, reduced blood sugar levels in a diabetic patient using a significantly reduced dosage of medication. Readers are referred to **US Patent # 11,077,052 B1** for trial details. This experiment definitively proved that probiotic therapy could function as an adjuvant alongside medicaments to lower or cure T2DM. Similar results have been observed by several investigators, although the exact mechanism was not always determined.

The number of diabetic cases is significantly increasing worldwide, and it can be controlled through the infusion of probiotics as a preventative measure. Although it can also be used both therapeutically or as an adjuvant in conjunction with the allopathic diabetic therapy.

7) CONTROL OF HYPERTENSION

The simple definition of blood pressure is the amount of force the blood uses to get through the arteries. It has been established that the normal blood pressure in adults should be below 120/80 mm Hg. Most people with high blood pressure will have no symptoms. Some of the causative factors for high blood pressure are stress, dysbiosis, obesity and diabetes etc. The results of hypertension are heart attacks, stroke, thrombosis, kidney problems, eye problems, dementia etc. According to the American Heart Association the stage one hypertension is 130-139 mm Hg Systolic/ Diastolic below 80 mm Hg, and stage two hypertension is if Systolic number is 140mm Hg or higher, and Diastolic number is 90 mm Hg or higher.

Lack of exercise and overeating leads to obesity. The inflammation goes up significantly due to obesity with the onset of excess cytokines in the body leading to hypertension. The current discussion is concentrated mainly on pathophysiology of hypertension and the role of probiotics to prevent or control or treat hypertension.

Although the pathophysiology of hypertension is multifactorial, in my opinion it is linked to dysbiosis, which is an imbalance in the gut microbiome leading to hypertension through several interconnected physiological mechanisms. These include oxidative stress, increased inflammation, and disruptions to the gut-brain axis, altered metabolite production, change in the gut permeability, and changes in the Renin Angiotensin-Aldosterone system. I would like to delve into the role of the Renin Angiotensin-Aldosterone system and Dysbiosis as the causative factors for inducing hypertension.[94-99]

7.1: Renin-Angiotensin-Aldosterone System

Angiotensinogen gets converted to Angiotensin-1 by the action of renin enzyme in the liver. Angiotensin Converting Enzyme (ACE) acts on Angiotensin-1 to produce Angiotensin-2. This Angiotensin-2 serves as a substrate to be acted by ACE-2 enzyme present in the blood vessels resulting in Angiotensin 1-7. The cumulation of Angiotensin-2 constricts the blood vessels and thus raise the blood pressure. If not corrected, the excess activity of Angiotensin-2 will damage the vascular endothelial cells through NADPH Oxidase and thus induce severe oxidation of the blood vessels resulting in blood clots. Such blood clots ultimately block the blood flow resulting in heart attacks and strokes. Angiotensin 1-7 has completely opposite effect of Angiotensin-2 in that it causes vasodilation of blood vessels to lower or maintain the blood pressure.

7.2: Role of Dysbiosis to induce Hypertension

If the composition of Gastrointestinal micro-flora is altered due to toxins or excess pathogenic micro-flora in relation to saprophytic and probiotic bacterial microflora, the GI tract endothelial cells gets damaged. Such damage results in the weakening of the gut, which can cause hypertension perhaps by disrupting the function of ACE-2 enzyme in the blood vessels. In addition, if the number of probiotic bacteria are significantly reduced in the GI tract, the intestinal peristalsis gets altered to result in constipation. Constipation encourages the growth of non-beneficial microflora, which can convert the amino acids histidine and Tyrosine to histamine and Tyramine. These amines tend to induce hypertension through severe vasoconstriction. Dysbiosis can also weaken the intestinal barrier by increasing its permeability allowing pathogenic bacteria and their products like lipopolysaccharides (LPS) into the blood stream triggering inflammation and endothelial dysfunction resulting in hypertension.

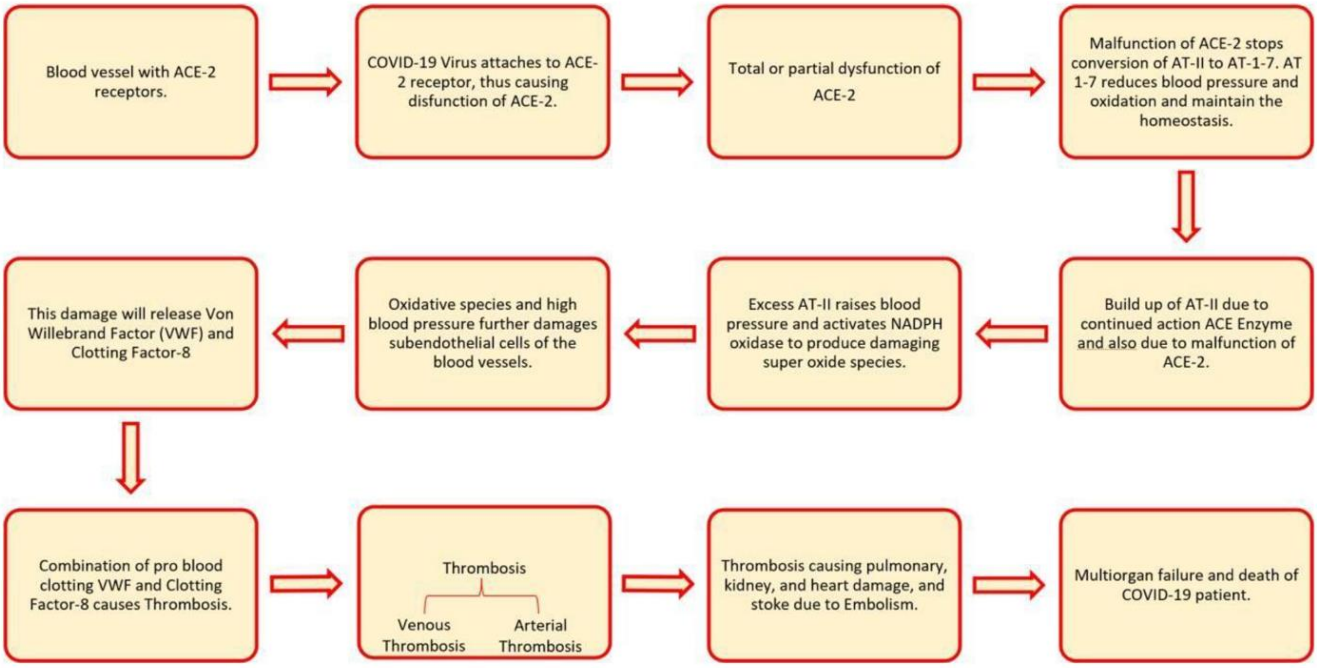
Dysbiosis increases the pro-inflammatory bacteria and a concomitant decrease in the anti-inflammatory bacteria. This imbalance will trigger a chronic inflammatory

response in the blood vessels resulting in vasoconstriction and hypertension.

Dysbiosis, by disrupting the microbial composition in the gut, can negatively alter the production of short chain fatty acids such as acetate and butyrate, which have anti-inflammatory and blood pressure lowering effects. It can also lead to the production of harmful metabolites due to the action of certain microbes in the GI tract, like Trimethylamine N-Oxide (TMAO) and hydrogen sulfide, which can promote vascular dysfunction and inflammation.

Dysbiosis can also disrupt the gut-brain axis communication (gut microbiome interaction with nervous system), which can affect the hormones (cortisone) to elevate blood pressure, thus inducing hypertension. For easy understanding the pathophysiology of hypertension due to disruption of hormonal- enzyme dependent vascular homeostasis due to SARS-CoV-2 corona viral infection is illustrated in Fig.10.

FIGURE 10: Pathophysiology of Hypertension in Blood Vessels Due to COVID-19 Viral Infection Through the Disruption of Hormonal Enzyme-Dependent Vascular Homeostasis, Resulting in Thrombosis and Multiple Organ Failure.



7.3: How do Probiotics reduce Hypertension?

Out of 100 trillion bacteria in the GI tract, roughly 20 trillion can be categorized as probiotics. I have listed several of these probiotic bacteria and their therapeutic effects earlier in this article. Probiotics and their immunomodulins can recognize pathogenic bacteria with the aid of receptors on their cell walls called "Pattern Recognition Receptors" (PRR5) to recognize pathogen associated molecular patterns (PAMPS) on the surface of the pathogenic bacteria. After recognizing the pathogens, probiotics trigger their own immune mechanism to inhibit or destroy the pathogens, through production of antimicrobial agents. In addition, they also compete for nutrients and the attachment sites in the GI tract thus outcompeting pathogenic bacteria. Thus, probiotics can correct the dysbiosis to reduce or eliminate inflammation to control hypertension.[89-99]

In addition, probiotics also stimulate the immune system to eliminate inflammation by enhancing the anti-inflammatory cytokines such as IL-10 and TGF-beta. At the same time, probiotics significantly reduce the pro-inflammatory cytokines such as IL-6 and TNF-alpha. In addition, probiotics play a significant role in orchestrating immune modulation with the aid of T-regulatory cells. The immunomodulins or the growth end products of probiotics can up regulate the production of ACE-2 enzymes to convert angiotensin-2 into angiotensin 1-7, thus, to increase vasodilation and retard the oxidation by the NADPH oxidase enzyme to protect the blood vessels from hypertension.

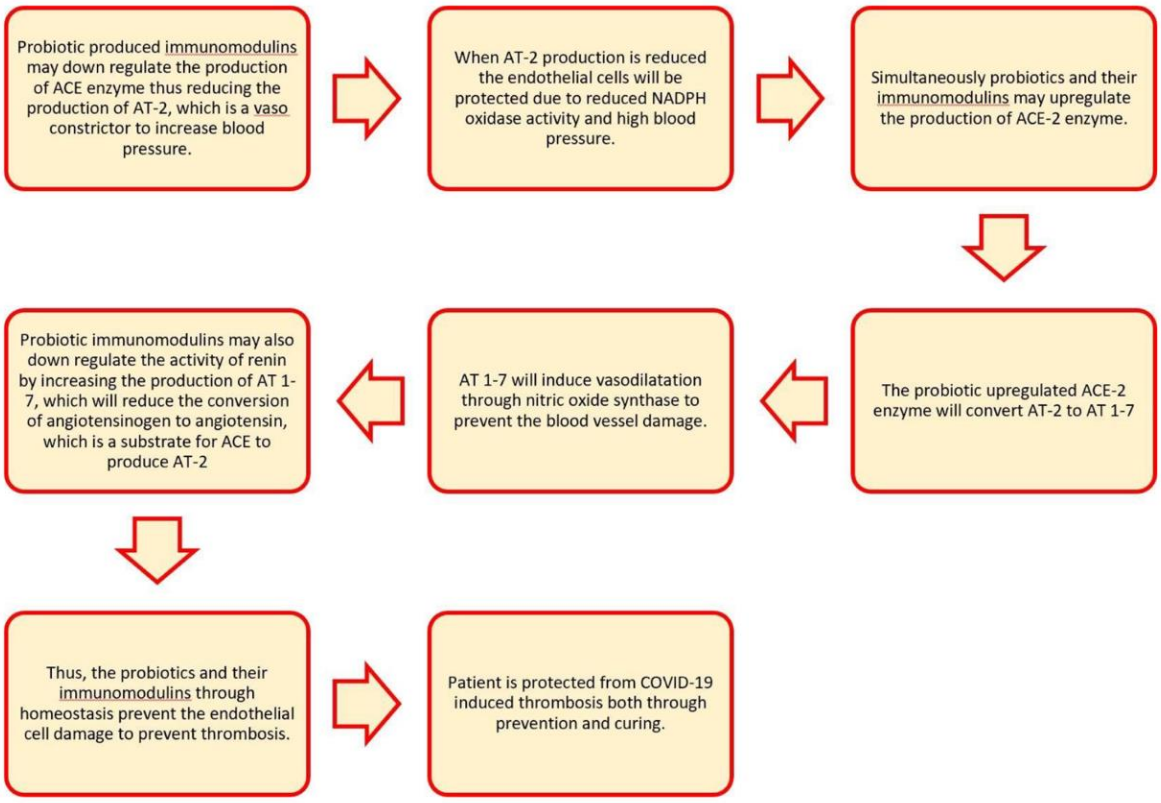
It has also been cited in the literature that probiotics significantly reduce the production of angiotensin-2 from angiotensin-1 by down regulating the production of angiotensin converting enzyme (ACE), to reduce the excess buildup of angiotensin-2, which is a vasoconstrictor.

Probiotics through production of short chain fatty acids protect the intestinal epithelial cell barrier from letting the entry of the vasoconstriction inducing toxins into the blood to protect the host from hypertension. In addition, probiotics reduce constipation through improved peristalsis and also prevent conversion of amino acids (such as tyrosine) into hypertension creating amine (tyramine).

Probiotics also improve the absorption of calcium through maintaining the gut pH in the acid range to reduce the hypertension since bio- available calcium controls and maintains the blood pressure in the normal range. The

mechanism of how probiotics can prevent or control hypertension due to corona viral infection is presented next in Fig 11. Similar mechanisms can be exhibited by probiotics in various different viral infections besides Covid-19.

FIGURE 11: How Do Multiple-Mixed Strain Probiotics and Their Immunomodulins Maintain the Hormonal Enzyme-Dependent Vascular Homeostasis to Prevent or Cure Hypertension and Resulting Thrombosis Induced by SARS Cov-2 Viral Infection.



Figures 10 and 11 are reproduced from the following article by Dr. Malireddy S Reddy, published in the European Society of Medicines-Medical Research Archives (this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy, Malireddy. (2022). Mechanism of Thrombosis During COVID-19 Infection Due to SARS-CoV-2 Virus and its Variants, and a Clinically Proven Strategy to Combat with Probiotics and their Immunomodulins. Medical Research Archives. doi.org/10. 10.18103/mra.v10i9.3075.

7.4: Practical Illustration

As a practical illustration, a controlled experiment conducted during Covid-19 pandemic demonstrated that probiotics, along with their immunomodulins, reduced hypertension using a significantly reduced dosage of blood pressure medication. The details and data are presented in US Patent # 11,077,052 B1. It goes to prove that probiotics have a significant effect on treating hypertension when used as adjuvant therapy. In addition, probiotics can also be used as preventive therapeutic aids to eliminate or control blood pressure in normal healthy range.[161]

8) CONTROL OF OBESITY (BY PROBIOTICS)

Obesity is now recognized as a pathological condition and is associated with several diseases, including Type 2 Diabetes, Cancer, and Cardiac Anomalies. It has been both postulated and proven that gut microbiota significantly influences the onset of obesity. By 2030, it is estimated that 38% of the adult population will be overweight and 20% will be obese worldwide.[100-104]

The human gastrointestinal tract contains over 100 trillion microorganisms. Approximately 90% of the gut microbiota belongs to the phyla **Firmicutes** and **Bacteroidetes.** Firmicutes are typically Gram-positive, indicating they have thick layers of peptidoglycan in their cell walls, whereas Bacteroidetes are Gram-negative, with thin peptidoglycan layers sandwiched between two phospholipid bilayers. Thus, Bacteroidetes are difficult to inhibit compared to Firmicutes either with antibiotics or other inhibitory agents.

Research using the 16S rRNA amplification technique has tentatively shown that the ratio of Firmicutes to Bacteroidetes (F/B) plays a crucial role in determining the onset of either obesity or intestinal disorders, particularly Inflammatory Bowel Disease (IBD), which includes **Ulcerative Colitis (UC)** and **Crohn's Disease (CD).**
As a general rule:

- If the F/B ratio is significantly greater than that of one, the individual is more likely to develop obesity.
- If the F/B ratio is significantly less than one, the individual is more susceptible to intestinal disorders due to inflammation and cytokine storms.

Example Scenarios:

- If Firmicutes count is 1,000,000 and Bacteroidetes count is 500,000, the F/B ratio is 2, which is above the set point of 1 and indicates obesity risk.
- Conversely, if Firmicutes count is 500,000 and Bacteroidetes count is 1,000,000, the F/B ratio is 0.5, which may lead to inflammation in the gastrointestinal tract, leading IBD.

Rule of Thumb: Maintaining a roughly equal number of Firmicutes and Bacteroidetes (F/B ≈ 1) is optimal for gut health.

High-fat diets tend to promote the growth of Firmicutes while decreasing the growth of Bacteroidetes. This microbial imbalance increases plasma **lipopolysaccharides (LPS)**, which contributes to obesity by activating **TLR-4** and upregulating pro-inflammatory cytokines. On the other hand, increasing Bacteroidetes enhances endogenous production of **Glucagon-Like Peptide-2 (GLP-2)** and strengthens intestinal tight junctions, thereby reducing LPS absorption and preventing obesity. However, excessive Bacteroidetes can also cause intestinal irritation due to a significant reduction in Firmicutes.

The optimal F/B ratio, therefore, lies close to **1:1**, balancing the benefits of both phyla.

8.1: Determining the F/B Ratio:

The F/B ratio can be assessed using Gram staining of fecal samples under a microscope:

- Gram-positive (Firmicutes): purple
- Gram-negative (Bacteroidetes): red

Examples to determine the F/B ratio under microscope in a given field:

- 10 purple and 10 red bacteria = 1 (ideal)
- 15 purple and 5 red → F/B = 3 (indicative of obesity)
- 5 purple and 15 red → F/B = 0.33 (indicative of dysbiosis)

F/B ratios can be easily estimated through serial dilutions of fecal samples, which can be viewed accurately upon gram staining under microscope.

8.2: Probiotics and Their Role in Restoring the F/B Ratio

Controlling dysbiosis caused by excess Firmicutes through several mechanisms:[105-109]

A. **Direct inhibition** of Firmicutes overgrowth.
B. **Improving gut barrier integrity** to reduce LPS absorption.
C. **Inducing anti-inflammatory cytokines** such as IL-10 and TGF-beta while suppressing pro-inflammatory cytokines like IL-6 and TNF-alpha.
D. **Nutritional competition** to maintain a balanced F/B ratio.
E. **Production of bacteriocins** to selectively inhibit excess Firmicutes.
F. **Generation of short-chain fatty acids (SCFAs)** to strengthen the intestinal lining.
G. **Immunomodulation** to suppress inflammation.
H. **Encouraging Bacteroidetes growth** when F/B ratio is significantly higher than 1 by inhibiting Firmicutes selectively.
I. **Probiotic strains like *Lactobacillus rhamnosus*** have shown effectiveness in reducing the F/B ratio to correct obesity. Similarly, ***Saccharomyces boulardii*** helps reverse obesity by modulating the F/B ratio.

8.3: Controlling excessive Bacteroidetes to Optimize the F/B Ratio

Increased Bacteroidetes in comparison to Firmicutes, can also lead to immunological disorders. These bacteria may adhere to mucosal epithelial cells, triggering inflammatory responses and inducing **TNF-alpha** production by monocytes and macrophages. Suppressing TNF-alpha by proper probiotics can lead to remission in IBD patients.

SCFAs produced by probiotics promote the secretion of **IL-10**, an immunosuppressive cytokine, by T-effector cells.

Most studies show:

- **Bacteroidetes** exhibit **pro-inflammatory** properties via endotoxins.
- **Firmicutes** display **anti-inflammatory** effects and help slow IBD progression.
- Selective beneficial probiotics can offset the ill effects created by such dysbiosis.

8.4: Examples of beneficial probiotics:

- *L. rhamnosus*, *L. paracasei*, *L. salivarius*, and *S. boulardii* are effective when the F/B ratio is high (obesity-related) to bring to the optimal level to correct obesity.
- *L. reuteri*, *L. plantarum*, *L. casei*, *L. acidophilus*, Bifidobacterium bifidum, and B. lactis help when the F/B ratio is low (IBD-related), to correct the intestinal inflammation.

In conclusion, understanding the F/B ratio is key to managing obesity and intestinal disorders. **Multiple mixed strain probiotics** along with their immunomodulins can dynamically adjust the microbiota composition through **immune modulation**, helping either increase or decrease the F/B ratio as needed. Dysbiosis and altered F/B ratios are now also implicated in **long COVID**, reinforcing the importance of microbiome balance.

Thus, **multiple mixed strain probiotic therapy**, in combination with proper nutrition and exercise, is a powerful tool in managing **obesity, and other intestinal disorders**, as an essential therapeutic aid in both preventive and clinical medicine settings.

9) PREVENTION AND CONTROL OF ALLERGIES

Food allergies have become a common public health problem. It can be classified into IgE-mediated, non-IgE-mediated, and mixed IgE-mediated types. In general, clinical practice, IgE-mediated allergies are more common. Approximately 4% of Americans are affected by IgE-mediated food allergies, and the prevalence is as high as 8% in children. Globally, between 10% (800 million) and 40% (3.2 billion) of the population are affected by some form of allergy. Allergies are more

prevalent in Western countries than in Asian countries. The "Hygiene Hypothesis" suggests that reduced exposure to microbes in early childhood may contribute to higher allergy rates in Western populations.[122]

An allergy is an adverse immune reaction to normally harmless substances known as allergens. When an allergic individual is exposed to an allergen, their immune system overreacts, causing various symptoms such as sneezing, itchy eyes, wheezing, runny nose, hives, and even life-threatening anaphylaxis. It is important not to confuse food allergies with food intolerances. For instance, lactose intolerance is not a food allergy, while a reaction to casein (a milk protein) is considered an allergy. Allergic reactions typically appear quickly, whereas symptoms of intolerances take longer to manifest.

When someone (with allergies) is exposed to an allergen, their immune system produces specific IgE antibodies against that allergen. This IgE production results from the overactivity of TH2 immune cells. These IgE antibodies bind to mast cells and basophils, priming them for a reaction. Upon re-exposure to the same allergen, the allergen cross-links with the specific IgE on the primed mast cells and basophils, leading to their degranulation and the release of inflammatory mediators such as histamine. These mediators are responsible for the symptoms associated with allergic reactions.

When a partially digested protein (long-chain peptide) enters the bloodstream through the gastrointestinal (GI) epithelial cells, it acts as an antigen, triggering the production of IgE antibodies specific to that peptide. When a similar peptide (antigen) is introduced again, an antigen-antibody reaction occurs on the primed mast cells, releasing inflammatory mediators and causing allergy symptoms. However, if the protein is fully digested to the point of liberating individual amino acids or the intestinal epithelial cells effectively block peptide entry, the allergic reaction does not occur.[110,1`17,121]

Physiological role of probiotics to prevent or reduce allergies

Probiotics can prevent or control allergies through the following mechanisms:[111-120]

1. **Strengthening the Gut Barrier:** Probiotics produce short-chain fatty acids (SCFAs), which significantly strengthen intestinal cell walls, thereby preventing the entry of allergens.[123]
2. **Blocking Allergen Adhesion:** Probiotics adhere to the mucosal membranes, preventing allergens from binding to or being absorbed in the GI tract.[124]
3. **Protein Digestion:** Probiotic-derived proteases and aminopeptidases digest proteins into amino acids, eliminating major peptide antigens that would otherwise be absorbed in the GI tract.
4. **Modulating Immune Response:** Probiotics shift the TH1/TH2 balance more toward TH1, reducing the overactivity of TH2 cells that promote IgE production and allergic responses.[125-127]
5. **Reducing Allergy-Related Cytokines:** Certain probiotic strains reduce TH2-associated cytokines such as IL-4, IL-5, and IL-13, which play key roles in allergic reactions.
6. **Increasing Anti-Inflammatory Cytokines:** Probiotics increase IL-10 production, an anti-inflammatory cytokine that helps regulate immune responses and reduce allergic symptoms.[133-`136]
7. **Enhancing Regulatory T Cells:** Some probiotics promote the activity of regulatory T cells (T-regs), which suppress excessive immune responses and help maintain immune tolerance.[147-151]
8. **Promoting TGF-beta Secretion:** Strains like *L. reuteri* and *L. paracasei* enhance the secretion of TGF-beta (an anti-inflammatory cytokine), which induces T cell differentiation into Tregs to support immune tolerance.
9. **Suppressing Pro-Inflammatory Cytokines:** *L. plantarum* inhibits IL-6 and TNF-alpha while upregulating IL-10, thereby reducing adverse immune activation.
10. **Activating TH1 and Tregs:** *L. acidophilus* activates TH1 and regulatory T cells, promoting immune tolerance and reducing allergic reactions.
11. **Regulating Gut Microbiota:** *Bacillus coagulans* and *Bifidobacterium longum* alleviate food allergies by optimizing the gut microbiota, particularly by balancing the Firmicutes/Bacteroidetes ratio.
12. **Cell Wall Polysaccharides:** Polysaccharides from *Propionibacterium* and *Bacillus* cell walls stimulate T cells to secrete IL-10 and induce the production and activity of regulatory T cells, helping to establish immune tolerance, which can simmer the allergic response or allergy.[128-132, 137-142]

Each specific probiotic strain exhibits unique functions through the production of immunomodulins. Therefore, using a **multiple mixed strain probiotic formulation** with their respective immunomodulins is considered the best practice for preventing or managing allergies.

Although probiotic therapy is an excellent preventive and long-term management strategy for allergies, it should complement clinically proven allergy treatments, especially in cases involving sudden-onset or life-threatening symptoms.

10) IMPROVING ANTI-AGING (PROBIOTICS)

Generally, people believe that anti-aging cannot be accomplished unless they go through severe medications. In reality, this is not true. Anti-aging can be achieved naturally by improving immunity, maintaining a healthy gastrointestinal (GI) microbiota, exercising regularly, fostering a positive mental attitude, practicing meditation, and ensuring proper nutrition. All of these approaches are closely linked to the GI microbiota and microbiome, as they regulate and orchestrate the immune system's primary factor in slowing the aging process.[153] This section is dedicated to the mechanisms and physiology behind the therapeutic use of probiotics in promoting anti-aging.

The human GI tract contains over 100 trillion organisms, representing more than 1000 genera and species, collectively referred to as the microbiota. Healthy gut microbiota can naturally transition into dysbiosis as part

of the aging process. One way to prevent this age-related dysbiosis is through the regular or periodic administration of carefully selected multiple mixed-strain probiotics, along with their immunomodulins.

It is plausible to suggest that during aging, the Firmicutes/Bacteroidetes (F/B) ratio tends to fall significantly below 1, thereby increasing susceptibility to severe diseases. Aging individuals also tend to lose muscle mass (sarcopenia), which may result from reduced nutrient uptake and sluggish digestion. Although the enzymatic systems of the GI tract slow down with age, proper maintenance of the microbiota—both in terms of microbial composition and population—can compensate for this decline. Enzymes produced by microbiota can offset the loss of the host's own digestive enzymes. This phenomenon is also seen in monogastric animals.

A classic example is the enzyme lactase (β-galactosidase), produced by GI epithelial cells, which digests the disaccharide lactose. The gene responsible for lactase production becomes less active or ceases expression with age, leading to lactose intolerance and resulting in severe GI disorders. Additionally, this can interfere with calcium absorption due to an unfavorable pH, leading to osteopenia, osteoporosis, and abnormal hypertension.

In old age, dysbiosis could also cause more frequent intestinal infections, disrupt the gut-brain axis, lower peristalsis (leading to constipation), and increase the conversion of procarcinogens into carcinogens, thereby raising the risk of colorectal cancer.[152]

The administration of multiple mixed-strain probiotics along with their immunomodulins can help counteract immunosenescence associated with aging. Probiotics also help maintain the optimum F/B ratio, thereby reducing systemic inflammation. Consequently, maintaining a healthy microbiota is crucial for promoting longevity and combating age-related decline.[154-160]

The Nobel laureate Dr. Elie Metchnikoff, in his 1907 Nobel lecture, stated that long life could be achieved through the maintenance of GI tract flora via the periodic oral administration of lactic acid-producing bacteria of the genus *Lactobacillus*. Literature also reports that Russians who regularly consumed fermented milk products lived up to 140 years. The late Dr. Marvin Speck of North Carolina State University also advocated the daily consumption of *Lactobacillus acidophilus* to promote health and thus longevity, perhaps based on observations of certain African tribes with long life spans who consumed fermented drinks with unidentified genera of Lactic acid bacteria, as part of their diet.

Exercise and a positive mental attitude are the essential practices for anti-ageing. Since immunosenescence is unavoidable in old age, every positive precaution must be undertaken to uplift the immune system. The essential factor which controls and maintains the optimal immune system is the proper Microbiota and the resulting Microbiome. The best possible probiotics to override the advanced age-related dysbiosis are *Lactobacillus acidophilus, L. casei, L. Helveticus, L. Bulgaricus, Lactococcus lactis var. lactis* and *Saccharomyces boulardi*. Of course, the role of species of the genus *Propionibacterium, Enterococcus faecium, Bifidobacterium bifidus* and *Streptococcus thermophilus* are essential to maintain the overall optimum composition of Microbiota to improve anti-ageing.

11) PREVENTION/ TREATMENT OF HOSPITAL-ACQUIRED INFECTIONS (BY PROBIOTICS)

In recent years, hospitals have become breeding grounds for multiple antibiotic-resistant bacteria, such as *Clostridium difficile* (C. diff), MRSA (*Methicillin-resistant Staphylococcus aureus*), *Klebsiella*, and various pathogenic viruses, including SARS-CoV-2, the virus responsible for the COVID-19 pandemic. A patient may enter a hospital for treatment of a primary condition—such as heart disease, kidney disease, or another illness—only to contract a secondary, often more dangerous, infection caused by antibiotic-resistant pathogens. These infections, known as nosocomial or hospital-acquired infections, can be deadlier than the original illness.[161,162]

Development of Multiple-Antibiotic Resistance by Pathogenic Bacteria to Become Superbugs

In 1927, Nobel Laureate Dr. Alexander Fleming discovered the first antibiotic—penicillin—produced by the *Penicillium* mold to inhibit a wide range of pathogenic bacteria. In 1945, British Prime Minister Winston Churchill approved the commercial use of penicillin to protect wounded soldiers from sepsis during World War II. It was hailed as a miracle drug and saved millions of lives.

However, the extensive use of penicillin led to a new problem: pathogenic bacteria began to develop resistance by acquiring extrachromosomal genes that coded for enzymes capable of inactivating penicillin. In response, the pharmaceutical industry developed several improved antibiotics—such as tetracycline—to counter these resistant microorganisms.

Yet, as Sir Isaac Newton famously said, "For every action, there is an equal and opposite reaction." Over the decades, the widespread use of antibiotics has resulted in the emergence of superbugs—such as MRSA and C. *diff*—that exhibit resistance to multiple antibiotics through various mechanisms. These superbugs now claim millions of lives annually. Projections suggest that by 2050, nosocomial infections could kill over 10 million people per year unless alternative treatments are found.[163]

A Promising Alternative: Probiotic Therapy

One such alternative is **probiotic therapy**, which may replace antibiotic therapy either completely or partially. An extensive study conducted at Iowa State University by the author of this article demonstrated that certain probiotic bacteria naturally resist several antibiotics while still offering significant health benefits.[166]

Dr. Reddy initiated a project to develop a multi-strain probiotic blend—combined with their immunomodulins—

to combat hospital-acquired infections. The success of this approach is attributed to the **biological inhibition** that probiotics exert against superbugs. It was discovered that the key factors responsible for this inhibition are not only the probiotic bacteria themselves but also the **immunomodulins** they produce. Among these are specific **bacteriocins** and therapeutic peptides that individual probiotic strains generate. These molecules exhibit species- and strain-specific physiological and therapeutic effects.[167,168,174]

To enhance therapeutic potential, a **multi-strain probiotic formulation** was developed using different genera and species of probiotics. This blend leverages diverse therapeutic principles to target superbugs using an all-natural approach. In addition, antibiotics such as Vancomycin and Bacitracin can be administered along with multiple mixed strain probiotics to treat nosocomial infections successfully.

The following tables and figures illustrate the composition of multiple mixed strain probiotics and their effect on preventing or treating hospital acquired infections[170,171,174]

- Table-2: The inhibitory effects of **individual probiotic strains** versus **multi-strain blends** against C. *diff*
- Table-3: The inhibitory effects of these same strains against **MRSA**
- Table-4: The inhibitory effect of Vancomycin and Bacitracin and combination of multiple mixed strain probiotics plus Vancomycin and Bacitracin on *Clostridium difficile* (C. diff).
- Table-5: The inhibitory effect of Vancomycin and Sulphamethoxyzole, and combination of multiple mixed strain probiotics plus Vancomycin and Sulphamethoxyzole on Methicillin Resistant Staphylococcus Aureus (MRSA).
- Figures 12-16: The outcomes of different treatments—**antibiotic alone, probiotic alone,** and **combination therapy**—in managing C. *diff* infection.
- Figure-17: The **preventive effect** of administering the multi-strain probiotic blend **prior to hospitalization,** aimed at reducing the risk of C. *diff* infection during hospital stay.

Table 2: The inhibitory effects of individual probiotic strains[a,b] versus multiple-strain probiotic blends against *Clostridium difficile (C.diff)*.

Probiotic Strain	Degree of inhibition on C. diff
A. Lactobacillus acidophilus	++
B. Bifidobacterium bifidus	+
C. Leuconostoc dextranicum	+
D. Sacchoromyces boulardii	++
E. Propionibacterium shermanii	+
F. Propionibacterium zeae	+
G. Lactobacillus sporogenes	++
H. Streptococcus lactis (ON)	++
I. Streptococcus cremoris (ON)	++
J. Streptococcus diacetilactis (ON)	++
Combination of the above A through J (multiple mixed strains Probiotics)	++++
ON – Old Nomenclature	

[a] New nomenclature – *Streptococcus lactis (old) – Lactococcus lactis var. lactis; Streptococcus cremoris (old) – Lactococcus lactis var. cremoris; Streptococcus diacetylactis (old) – Lactococcus lactis var. lactis subsp. diacetylactis*
[b] Key: + = slight inhibition; ++ = moderate inhibition; +++ = severe inhibition; ++++ = significant inhibition

The results presented in Table 2 clearly indicates that the degree of inhibition on multiple antibiotic-resistant C.*diff* pathogen by individual strains of probiotics varies due to variance in the immunomodulins they produce. The probiotic strains belonging to the genus *Lactococcus* and *Lactobacillus* exhibited more inhibition than *Propionibacterium* and *Bifidobacterium*. However, multiple mixed-strain probiotics where all the individual strains were blended, exhibited an exceptional inhibition on C.*diff* indicating, under laboratory conditions, that there is a synergistic effect among the probiotic strains, perhaps due to the interaction of immunomodulins that they have produced.

Table 3: The inhibitory effects of individual probiotic strains[a,b] versus multi-strain probiotic blends against Methicillin-resistant Staphylococcus aureus (MRSA).

Probiotic Strain	Degree of inhibition on MRSA
1. Lactobacillus bulgaricus	++
2. Lactobacillus acidophilus	++
3. Leuconostoc dextranicum	+
4. Brevibacterium linens	+
5. Propionibacterium zeae	+
6. Propionibacterium jensenii	+
7. Propionibacterium shermanii	+
8. Propionibacterium arabinosum	+
9. Lactobacillus sporogenes	+
10. Streptococcus lactis	++
11. Streptococcus cremoris	++
12. Streptococcus diactilactis	++
Combination of the above 1 through 12 (multiple mixed strain Probiotics)	++++

[a] New nomenclature – *Streptococcus lactis (old) – Lactococcus lactis var. lactis; Streptococcus cremoris (old) – Lactococcus lactis var. cremoris; Streptococcus diacetylactis (old) – Lactococcus lactis var. lactis subsp. diacetylactis*

[b] Key: + = slight inhibition; ++ = moderate inhibition; +++ = severe inhibition; ++++ = significant inhibition

The results indicate that *Lactobacillus sporogenes (Bacillus coagulans)* exhibited lesser inhibition on Methicillin-resistant *Staphylococcus aurease* (MRSA) in comparison to C.*diff*. Still, the inhibition exhibited by species of *Lactobacillus* and *Lactococcus* on MRSA was similar to what has been observed on C.*diff*. The multiple mixed-strain probiotics exhibited significant inhibition compared to the individual strains of probiotics employed. Once again indicating (under laboratory conditions) that there is a definite synergistic effect among strains of the multiple mixed-strain probiotics to inhibit both the multiple antibiotic-resistant pathogens causing hospital-acquired infections (nosocomial infections), C.*diff* and MRSA.

Table 4: The inhibitory effect of Vancomycin and Bacitracin and combination of multiple mixed strain products plus Vancomycin and Bacitracin on *Clostridium difficile (C.diff)*[a,b]

Component Tested	Degree of inhibition on C. diff
Vancomycin and Bacitracin	++
Vancomycin and Bacitracin, plus Leuconostoc dextranicum, Sacchoromyces boulardii Propionibacterium shermanii Streptococcus durans Lactobacillus sporogenes	++++

[a] New nomenclature – *Streptococcus durans (old) – Enterococcus faecium (new); Lactobacillus sporogenus (old) – Bacillus coagulans (new)*

[b] Key: + = slight inhibition; ++ = moderate inhibition; +++ = severe inhibition; ++++ = significant inhibition

The degree of inhibition exhibited by the combined antibiotics Vancomycin and Bacitracin on C.*diff* is far inferior to the inhibition exhibited by the combination of Vancomycin/ Bacitracin-resistant probiotics and the antibiotics Vancomycin and Bacitracin. It indicates that the hard-to-treat or advanced lethal cases of nosocomial infections caused by C.*diff* can be treated using the combination of specific antibiotics and multiple mixed-strain probiotics (in vivo).

Table 5: The inhibitory effect of Vancomycin and Sulphamethoxyzole, and combination of multiple mixed strain probiotics plus Vancomycin and Sulphamethoxyzole on Methicillin Resistant Staphylococcus aureus (MRSA).[a,b]

Component Tested	Degree of Inhibition on MRSA
Vancomycin and Sulfamethoxazole	++
Vancomycin and Sulfamethoxazole, plus Leuconostoc dextranicum Brevibacterium linens Lactobacillus bulgaricus Propionibacterium zeae Propionibacterium jensenii Propionibacterium shermanii Propionibacterium arabinosum Lactobacillus sporogenes	++++

[a] New nomenclature – *Lactobacillus sporogenus (old) – Bacillus coagulans (new)*
[b] Key: + = slight inhibition; ++ = moderate inhibition; +++ = severe inhibition; ++++ = significant inhibition

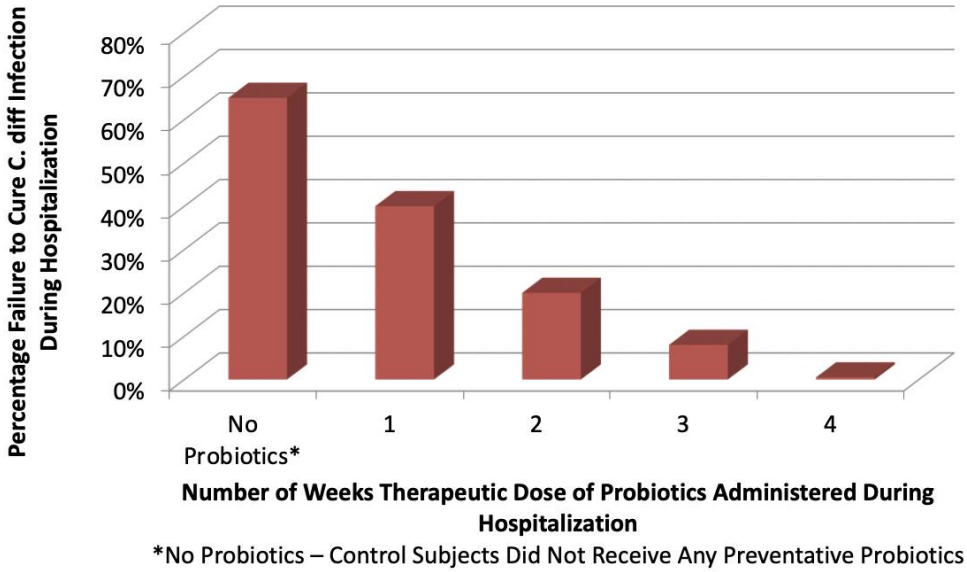
The degree of inhibition exhibited by the combined antibiotic Vancomycin and Sulfonamide, Sulphamethoxyzole on nosocomial infection causing multiple antibiotic-resistant MRSA is far inferior to the combination of Vancomycin plus Sulphamethoxyzole and the multiple mixed-strain probiotics (which are resistant to Vancomycin and Sulphamethoxyzole). Once again indicating that even the advanced severe cases of fatal nosocomial infections caused by MRSA can be treated by using the combination of specific probiotics and antibiotics plus Sulfonamides.

The results presented in Tables 2, 3,4 and 5 distinctly proves that the selected multiple mixed-strain probiotics significantly inhibited C.*diff* and MRSA pathogenic bacteria better than each individual probiotic strain. In addition, it was observed that selected multiple mixed-strain probiotics can be administered simultaneously with specific antibiotics and antimicrobials (to which probiotic strains are resistant) to treat the hospital-acquired infections under severe conditions.

Figures 12 through 16 depict the clinical results obtained by administering multiple mixed-strain probiotics to patients admitted to the hospital for treatment of C. *diff* infection. The preparation and dosage of the multiple mixed strains are presented in detail in a prior publication by the author of this article.[163]

The clinical data presented in Figure 12 clearly demonstrate the efficacy of administering multiple mixed-strain probiotics in curing or treating C. *diff* nosocomial infection.

FIGURE 12: The Effect of Multiple Mixed-Strain Probiotics and Their Immunomodulins on Curing *Clostridium difficile (C.diff)* infections When Administered During Hospitalizations, As a Therapeutic Aid (Without Antibiotics).



*No Probiotics – Control Subjects Did Not Receive Any Preventative Probiotics

Figure 13 compares the effect of antibiotics versus multiple mixed-strain probiotics in treating C. *diff* infection. The data show that antibiotics alone were ineffective, whereas the probiotics completely cured the infection after four weeks of treatment, with noticeable progress beginning in the first week.

FIGURE 13: The Effect of Multiple Mixed-Strain Probiotics and Their Immunomodulins on Curing *Clostridium difficile (C.diff)* infections When Administered As a Therapeutic Aid (Probiotics Alone) vs. Antibiotic Therapy (Antibiotics Alone).

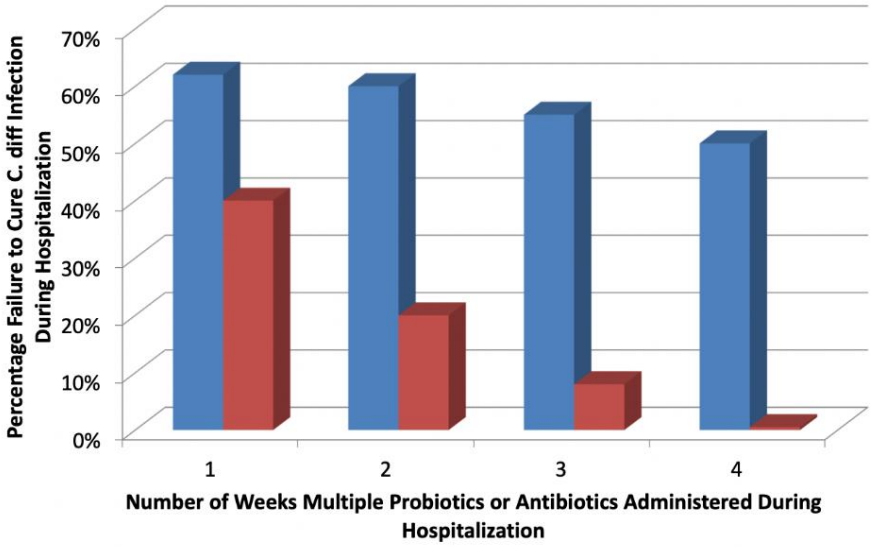


Figure 14 shows the results of combining antibiotics with multiple mixed-strain probiotic therapy. A significant reduction in C. *diff* infection was observed from the first week, with total remission by the third week. These results indicate that properly selected antibiotics, when used in combination with antibiotic-resistant multiple mixed-strain probiotics, can accelerate the treatment of C. *diff* infection.

FIGURE 14: The Effect of Multiple Mixed-Strain Probiotics and Their Immunomodulins on Curing *Clostridium difficile (C.diff)* infections When Administered During Hospitalization As a Therapeutic Aid, Along With Antibiotics (Vancomycin and Bacitracin).

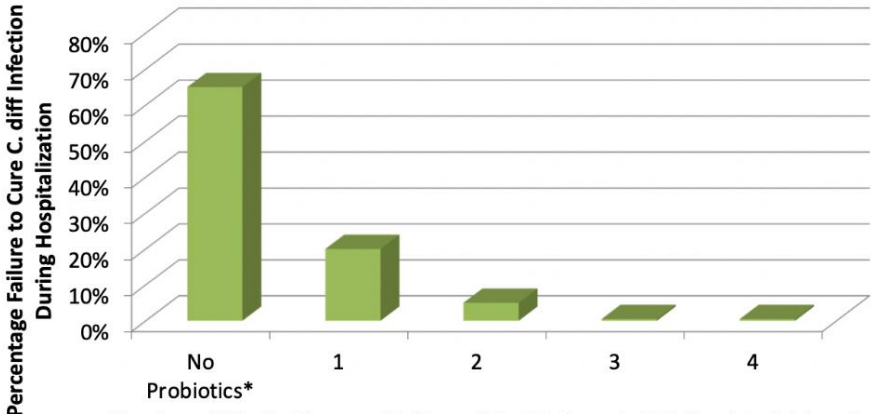


Figure 15 clearly illustrates the ineffectiveness of antibiotics in treating multiple antibiotic-resistant C. *diff* infection. This is one of the reasons why so many innocent people are dying annually due to the multiple antibiotic-resistant pathogenic bacteria, C.*diff*.

FIGURE 15: The Effects of Antibiotics Only On Curing *Clostridium difficile (C.diff)* Infections When Administered During Hospitalization as a Therapeutic Aid (Without Multiple Mixed-Strain Probiotics and Their Immunomodulins).

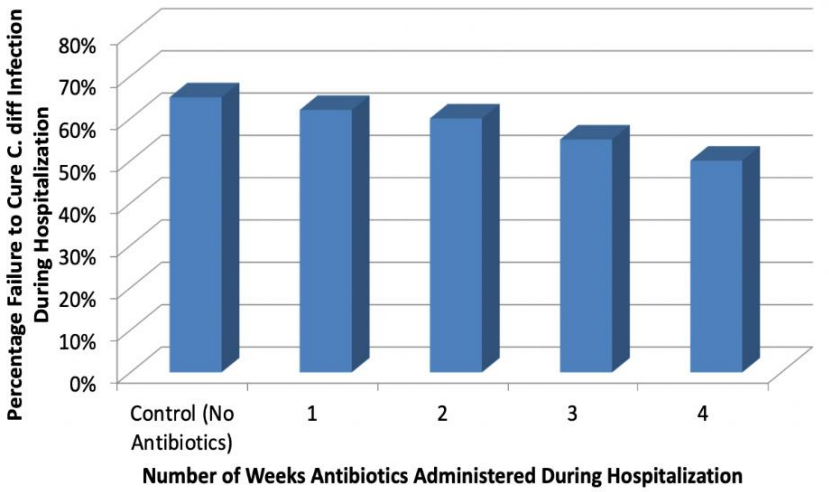
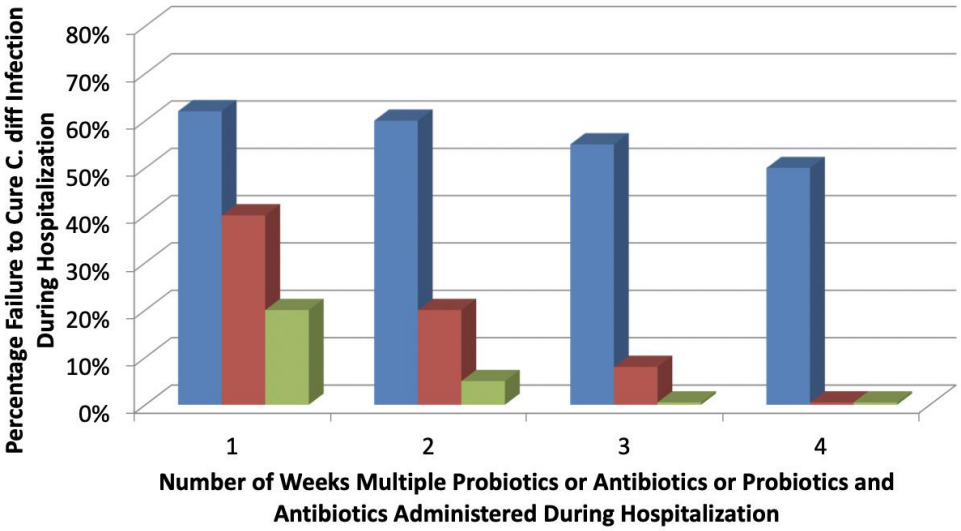


Figure 16 emphasizes the superior efficacy of multiple mixed-strain probiotics, alone and in combination with antibiotics, in treating C. *diff* infection. While probiotics alone cured the infection by the fourth week, the combination therapy began showing results from week one, with complete cure by the third week. It indicates that under severe lethal terminal cases of nosocomial infections, the combination of selective antibiotics and multiple mixed-strain probiotics can be used to protect the patient.

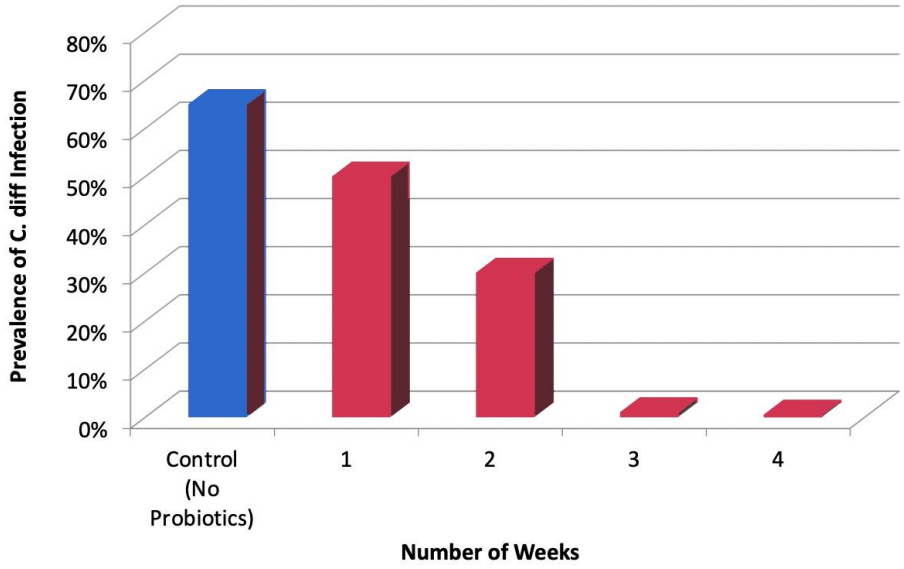
FIGURE 16: The Effect of Multiple Mixed-Strain Probiotics and Their Immunomodulins on Curing *Clostridium difficile (C.diff)* infections When Administered As a Therapeutic Aid (Probiotics Alone) vs. Antibiotic Therapy (Antibiotics Alone) vs. Mixed Probiotics and Antibiotic Therapy.



These clinical trials clearly demonstrate the efficacy of multiple mixed-strain probiotics in curing deadly hospital-acquired infections. Furthermore, the results confirm that combining antibiotics with probiotic therapy significantly enhances the speed of recovery from C. *diff* infection.

Figure 17 presents the effect of administering multiple mixed-strain probiotics prior to hospitalization in preventing C. *diff* infection. The results clearly indicate that a preventive dose of probiotics, along with their immunomodulins administered three weeks before hospitalization, completely prevented the onset of C. *diff* infection—even during a 3–4-week hospital stay. Thus, it is proven beyond doubt that multiple mixed-strain probiotics can serve both as preventive and therapeutic agents for controlling or treating nosocomial infections.

FIGURE 17: The Effect of Multiple Mixed-Strain Probiotics and Their Immunomodulins on *Clostridium difficile* Infections (in Red) When Administered Prior to Hospitalization v. Control Subjects with no probiotics (Blue).



Figures 12, 13, 14, 15, 16 and 17 are reproduced from the following article by Dr. Malireddy S Reddy, published in the International Journal of Pharmaceutical Sciences and Nanotechnology (this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy MS. Scientific and medical research on Dr. M.S. Reddy's multiple mixed strain probiotic therapy and its influence on assisting to cure or prevent the nosocomial infections, synergistically enhancing the conventional cancer therapies, as an adjuvant, and its possible potential to prevent or cure COVID-19 novel Coronavirus infection by balancing the intestinal microbiota and microbiome through modulation of the human immune system. Int J Pharm Sci Nanotech. 2020;13(3):4876-4906.

The following figures 18, 19, and 20 illustrates the hypothetical molecular mechanisms involved in inflammation due to nosocomial infection caused by Clostridium Difficile (C. *diff*) and how probiotics nullify inflammation through orchestrated immunomodulation.

Figure 18 clearly depicts that the Multiple antibiotic resistant C.*diff* not only destroys the GI tract epithelial cells through toxin production but also creates excess immunostimulation through the activation of TH-1 and TH-2 cells and IL-2, IL-4, IL-6 and IL-12 interleukins. They simultaneously suppress the production of TGF-beta and retinoic acid and increase the production of pro-inflammatory cytokine TGF-beta, ultimately inducing severe inflammation, which results in aggravating the disease symptoms associated with nosocomial infection, such as bloody diarrhea, intestinal irritation, etc., which ultimately leads to death.

FIGURE 18: A hypothetical molecular mechanism of how *Clostridium difficile* infection induces inflammation.

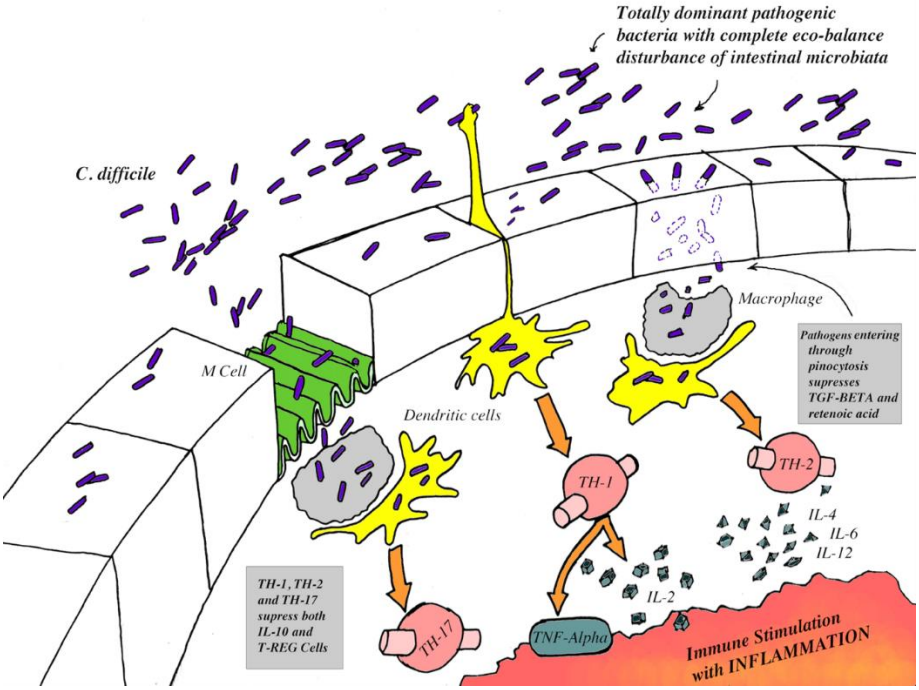
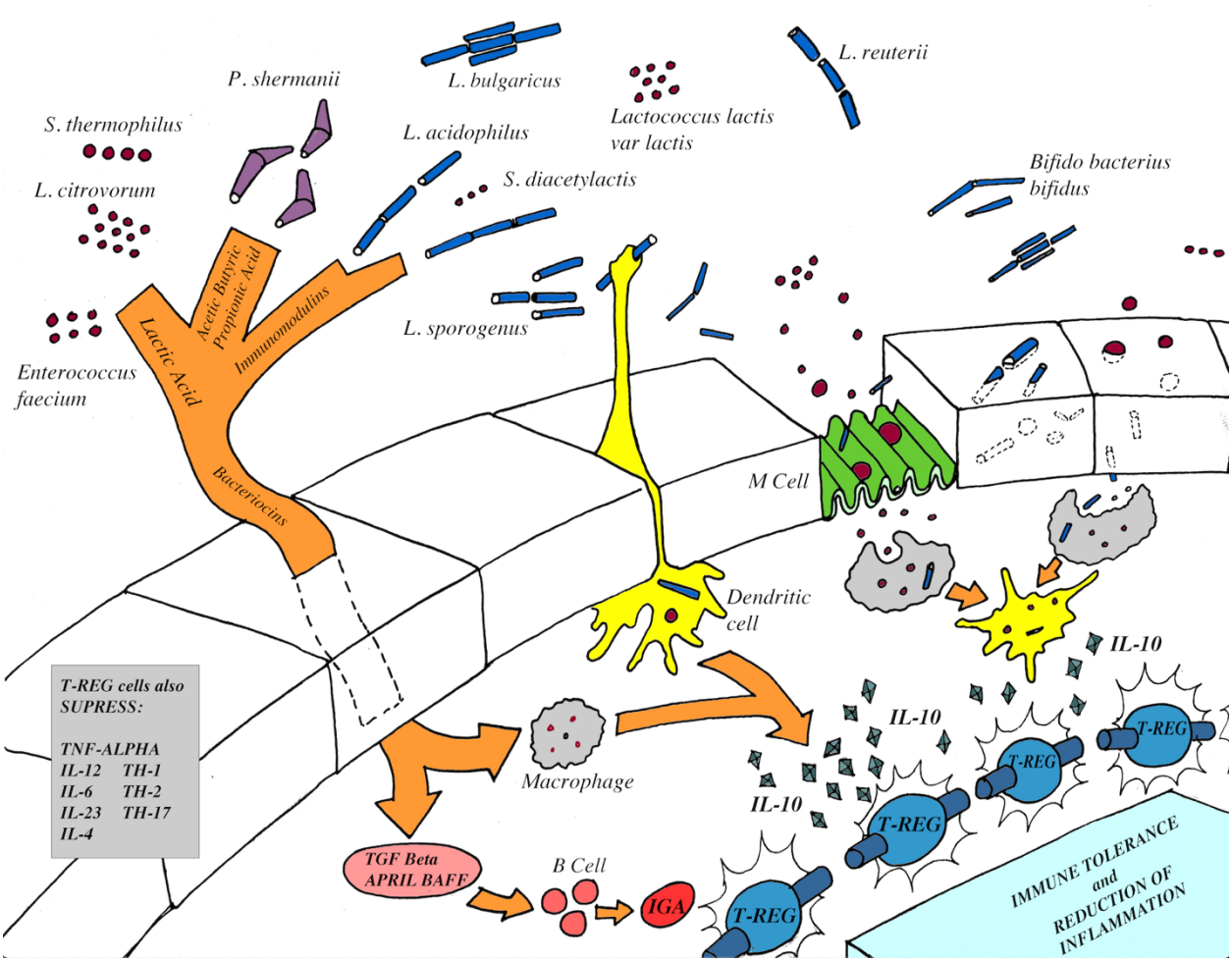


Figure 19 clearly demonstrates that the Multiple mixed strain probiotics and their immunomodulins maintains immune tolerance by inducing the production of IL-10 and T-Reg cells, in addition to enhancing the concentration of anti-inflammatory of cytokine TGF-beta, APRIL and BAFF, which ultimately stimulate the production of immunoglobulin A through B-cells of the lymphatic tissue. The entire immunomodulatory mechanism exerted by the multiple mixed strain probiotics acts as a preventive measure to protect the host from pathogenic nosocomial infections.

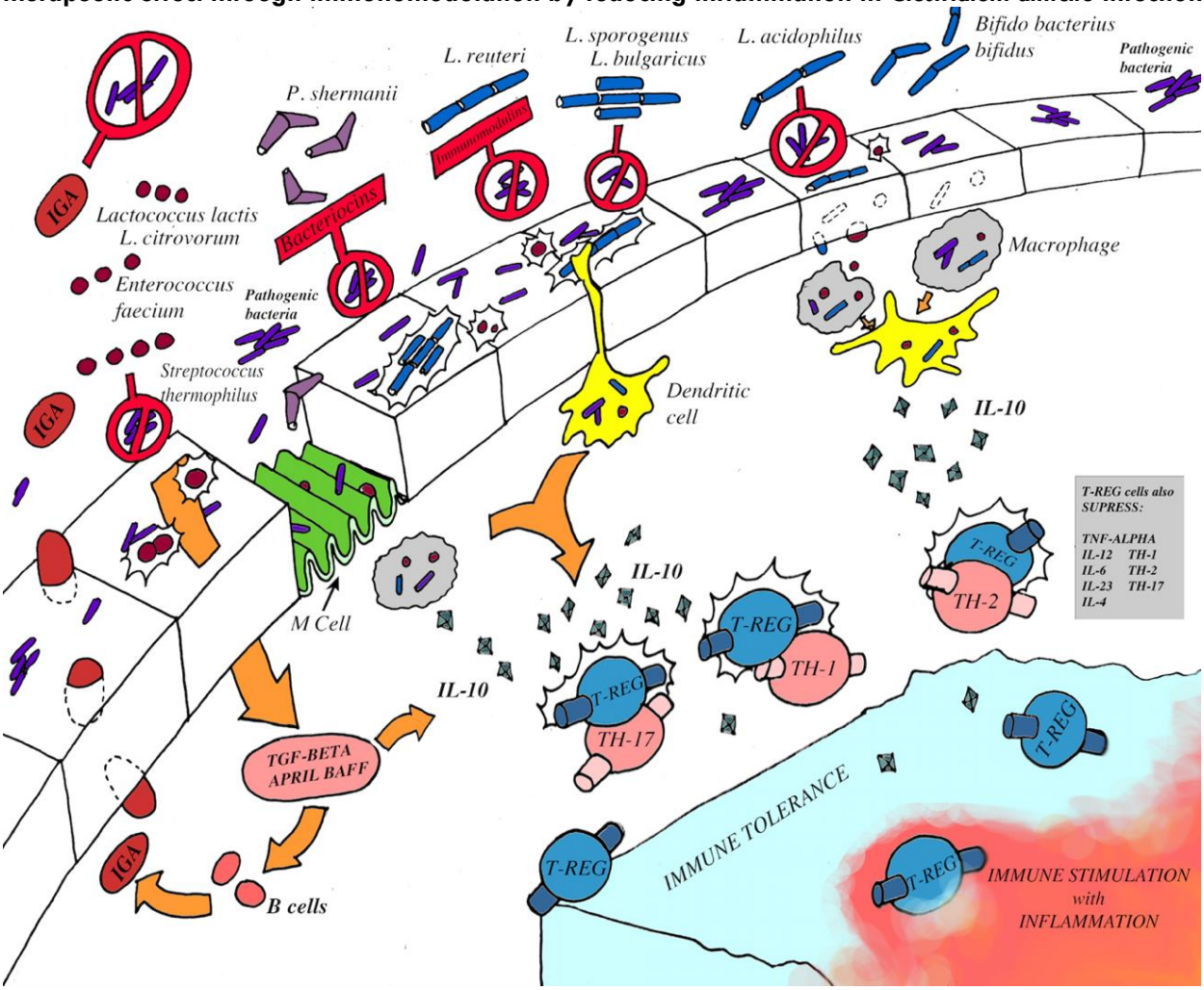
FIGURE 19: A hypothetical molecular mechanism illustrating how multiple mixed-strain probiotics reduce inflammation via immune tolerance, acting as a preventive measure against nosocomial *Clostridium difficile* infection.



The damage caused by C.*diff* organisms through TH-1, TH-2, and TH-17 cells and IL-A is precisely illustrated in Figure 20. In the same figure it is also illustrated regarding how multiple mixed strain probiotics can suppress the immune stimulation through the activation of T-Regulatory cells. Simultaneously the individual members of multiple mixed strain probiotics, such as species of the genus Propionibacterium, improves the intestinal tissue integrity through production of short chain fatty acids. In addition, the probiotic Streptococcus thermophilus inactivates the C.*diff* toxins. Probiotic Lactobacillus reuteri reduces the pain through the production of neurotransmitters-Gamma Amino Butyric Acid (GABA). Thus, the C.*diff* infection can be treated successfully with the aid of multiple mixed strain probiotics through reduction of the inflammation and simultaneously improving immunotolerance.

In addition, recently it has been proven for the first time that the probiotic-produced megamicroRNAs (memiRNAs) are responsible for not only inhibiting pathogenic bacteria in association with microRNAs of eukaryotic cells but also in controlling the strain dominance to prevent dysbiosis to improve the immunomodulation. Thus, the memiRNAs are categorized as part of the immunomodulins of probiotics.[175,17]

FIGURE 20: A hypothetical molecular mechanism showing how multiple mixed-strain probiotics exert their therapeutic effect through immunomodulation by reducing inflammation in *Clostridium difficile* infection.



Now one can appreciate the role of multiple mixed strain probiotics along with their immunomodulins to either prevent or treat the deadly hospital acquired infections.

12) PREVENTION OR SUPPRESSION OF CANCER (BY PROBIOTICS)

Although several treatment modalities and hypothesis elaborated on the genesis, pathophysiology, and curative aspects of cancer, I would like to concentrate on the role of probiotics and their immunomodulins as preventive or curative agents to curb cancer. Cancer starts due to mutation in a single cell and spreads, due to the inability of the immune system to recognize and kill it. If the immune system i.e. both innate and adaptive, is operating at maximum efficiency, cancer should not exist to create havoc in human life. Since probiotics and their immunomodulins have significant effects on activating and modulating the immune system, a major emphasis is placed on this segment of treatment modality.

Therefore, in this article, we will deal with this subject by outlining two different scenarios. The first scenario is the role of probiotics in preventing the conversion of procarcinogens into carcinogens in the GI tract through competing and curbing the microorganisms (involved in dysbiosis) responsible for producing enzymes which are responsible for such conversions. The second scenario is the role of probiotics to improve the efficiency of immune check point therapy and other cancer treatment modalities (up to 60%) in order to cure cancer with the least side effects and relapse.

12.1: Scenario 1, The Role of Probiotics and Their Immunomodulins to Prevent Dysbiosis-induced Microbial Conversions of Procarcinogens Into Carcinogens, Which are the Etiological Factors for the Genesis of GI Tract Cancers.

To start with, I would like to touch upon the available statistics on various causative factors of cancer. Recent global statistics on the etiology of cancer indicate the following:[172]

1. **30% of cancers are caused by tobacco abuse.**
2. **35% of cancers result from an unhealthy diet** that includes high fat intake and excess calories, ultimately leading to obesity, alcohol abuse, and a low intake of vitamins, minerals, and dietary fiber.
3. **17.5% are due to pathogens**, especially viral infections such as Epstein-Barr virus, Human Papillomavirus (HPV), and Hepatitis B or C.
4. **5% are attributed to hereditary causes**, i.e., inherited genes with carcinogenic properties.
5. **The remaining 12.5% are due to unknown factors**, possibly related to the side effects of drugs or environmental pollution.

Human beings are primarily responsible for 95% of this cancer epidemic—presumably due to a lack of understanding about the disease. This can be significantly improved through scientific knowledge, proper nutrition, a healthy lifestyle, and timely detection.

Since **35% of cancers are due to overeating or poor nutrition**, it is worth focusing attention on this area. In other words, indirectly, 35% of cancer cases are linked to the **gastrointestinal tract** and its associated **non-beneficial microflora.**

If you analyze the entire mechanism of cancer genesis and its lethal effects, cancer typically begins with a single cell undergoing mutation. It then progresses through a series of mutations until the host dies. However, if mutagens are reduced or eliminated from the body, cancer can be controlled. This reduction can be achieved if proper probiotics are administered in high doses and allowed to colonize the gastrointestinal tract.

In my opinion, a proper diet combined with probiotic therapy is the way forward in eliminating mutagenesis, the starting point of cancer. Any reduction of intestinal pH caused by probiotics can alter the activity of non-beneficial microbial flora, affect bile solubility, and decrease transit time. These changes help eliminate carcinogen-producing fecal bacterial enzymes and thus reduce the conversion of pro-carcinogens into carcinogens.

One of the therapeutic functions of probiotics is the suppression of cancer through modulation of intestinal bacteria. Some non-probiotic gastrointestinal flora can convert pro-carcinogens into carcinogens. Some end products of digestion are pro-carcinogenic. For example, the end products of digesting beef may be more pro-carcinogenic than those from a vegetable. While the pro-carcinogenic material may not cause cancer by itself, if acted upon by certain microbial enzymes in the GI tract, it can be converted into carcinogens.

Probiotics, by their innate nature, helps suppress the growth of undesirable enzyme-producing non-probiotic bacteria and thereby reduces the chances of converting pro-carcinogens into carcinogens. The following are some of the fecal (non-probiotic produced) enzymes responsible for the production of carcinogens and tumor promoters: **Beta Glycosidase, Beta Glucuronidase, Steroid 7 Alpha Dehydroxylase, Nitro-reductase, Nitrate Reductase, Azoreductase,** and **Tryptophanase**.

Beta Glycosidase: The human diet contains many plant glycosides, mainly flavonoids, which are poorly digested and reach the colon. There, the bacterial enzyme beta glycosidase hydrolyzes them to release sugar moieties for energy, leaving behind aglycones. Some of these plant-derived aglycones are mutagenic.

Beta Glucuronidase: This enzyme converts already inactivated glucuronidates (glucuronic acid plus carcinogens) in the GI tract into free carcinogens and glucuronic acid.

Steroid 7 Alpha Dehydroxylase: It converts non-carcinogenic primary bile acids into genotoxic and co-mutagenic secondary bile acids.

Nitrate Reductase: This enzyme reduces nitrate to nitrite, which is mutagenic and carcinogenic.

Azoreductase: This enzyme reduces food azo dyes to mutagenic aromatic amines and azo compounds.

Tryptophanase: It converts the non-carcinogenic amino acid tryptophan into the carcinogen indole.
All of the above fecal enzymes are produced by non-probiotic bacteria in the GI tract. They can be suppressed by maintaining a healthy population of probiotics through periodic ingestion or probiotic therapy using high doses.

Probiotics compete with both pathogenic and non-pathogenic bacteria through nutritional competence and by competitively excluding them from adhesion sites in the GI tract. Limited studies suggest that probiotics can suppress **group 1 carcinogenic bacterium**, *Helicobacter pylori*. They also decrease the virulence of intestinal pathogenic bacteria and viruses by creating unfavorable growth conditions—such as low pH—and by producing bacteriocins.

Due to the extensive proteolytic and acidogenic abilities of probiotics and their capacity to produce beneficial inducible enzymes, several mutagenic carcinogens can be deactivated and rendered harmless to the host.

In my opinion, the twenty-first century is the era for utilizing probiotics (beneficial microorganisms) as an essential part of drug therapy or other treatment modalities. This approach can reduce cancer and other molecular and metabolic diseases that are directly or indirectly associated with the gastrointestinal tract.

The latest discovery to treat cancer is through immune check point therapy. Even this therapy can only be effective at 20 to 30%, with the resultant unwanted side effects and relapse. Through extensive experimentation it was discovered that multiple mixed strain probiotics, when used as adjuvants can significantly improve the success of not only the immune check point therapy but also other standard cancer therapies due to their natural positive immunomodulation. The hypothetical mechanism has been presented with explicit details in this research communication.

12.2: Scenario 2: The Role of Probiotics and Their Immunomodulins to Improve the Efficacy of Current Cancer Treatment Modalities Through Probiotic-induced Modulation.

Under normal circumstances, T-cells detect non-self-elements in the body and destroy them through a chain of positive immune reactions. However, in the case of cancer, T-cells do not operate efficiently due to the heightened negative immune response triggered by immune inhibitor receptors belonging to the CD28 family.

Currently, the major immune inhibitor receptors known to suppress T-cell activity against cancer tissues are **PD-1** (*programmed death protein-1*) and **CTLA-4** (*cytotoxic T-lymphocyte-associated antigen 4*), both of which are surface molecules.[45,46,47]

Generally, tumor antigens generated by gene mutations are recognized by a non-defective, well-functioning immune system, which in turn generates specific **CD8+ cytotoxic T lymphocytes (CTLs)** that target tumor cells. These CTLs recognize and induce apoptosis in the tumor cells, thereby controlling cancer at its origin.

However, when the host immune system is compromised or when tumor cells exhibit poor immunogenicity, several adverse immunological events occur during cancer pathogenesis. Tumor cells adopt various strategies to evade immune attack—one of which is increasing **PD-L1** expression in tumor tissues to resist the cytotoxic effects of CTLs.

What prompts the expression of the PD-L1 ligand?

In the tumor microenvironment, T-cells become activated when antigen-presenting cells (APCs) recognize tumor neoantigens. These neoantigens, along with the major histocompatibility complex (MHC), are presented and bind to the T-cell receptor. Simultaneously, the co-receptor **CD28** binds to **CD80/CD86** ligands on the APCs. This interaction activates naive, tumor-specific T-cells, which begin producing **IFN-γ (interferon-gamma)**. IFN-γ then induces the expression of PD-L1 ligands on both cancer cells and other host immune cells.

Until PD-L1 expression occurs, the **PD-1 receptor**—a surface protein that regulates the adaptive immune response—remains inactive. Once PD-L1 ligands are expressed in significant quantities, they bind to the PD-1 receptors on activated T-cells. This PD-1/PD-L1 interaction results in T-cell dysfunction through mechanisms such as anergy, exhaustion, and apoptosis. This entire mechanism is presented with specific details schematically in Figure 21 and pictorially in Figure 22.

FIGURE 21: Schematic diagram illustrating PD-1 as a negative regulator of T-cells, which enhances ligand binding and interaction with T-cells.

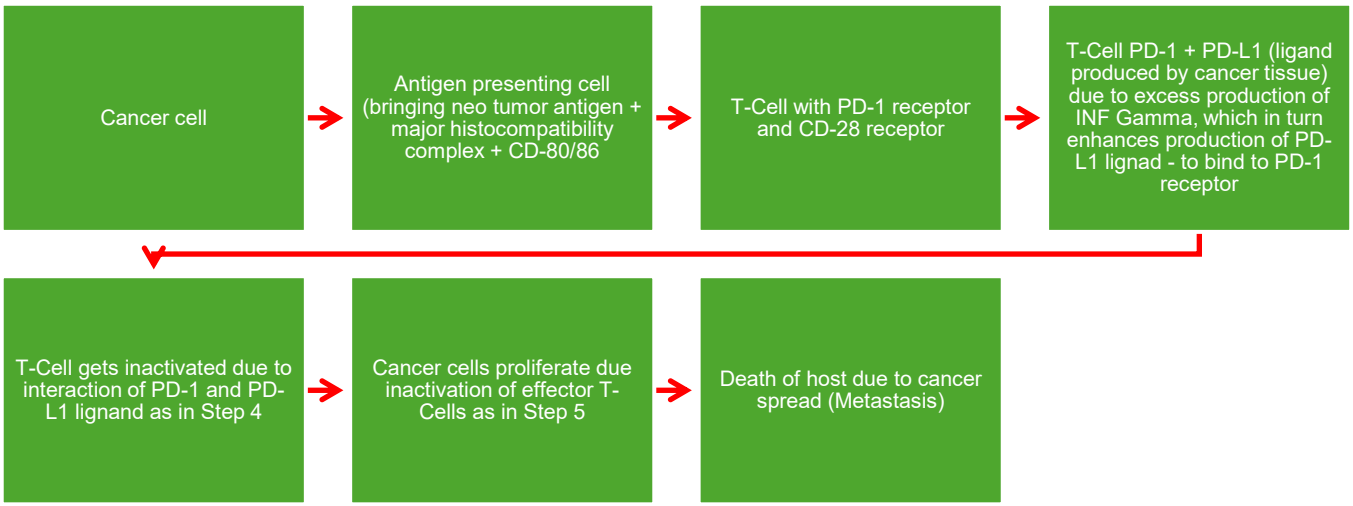
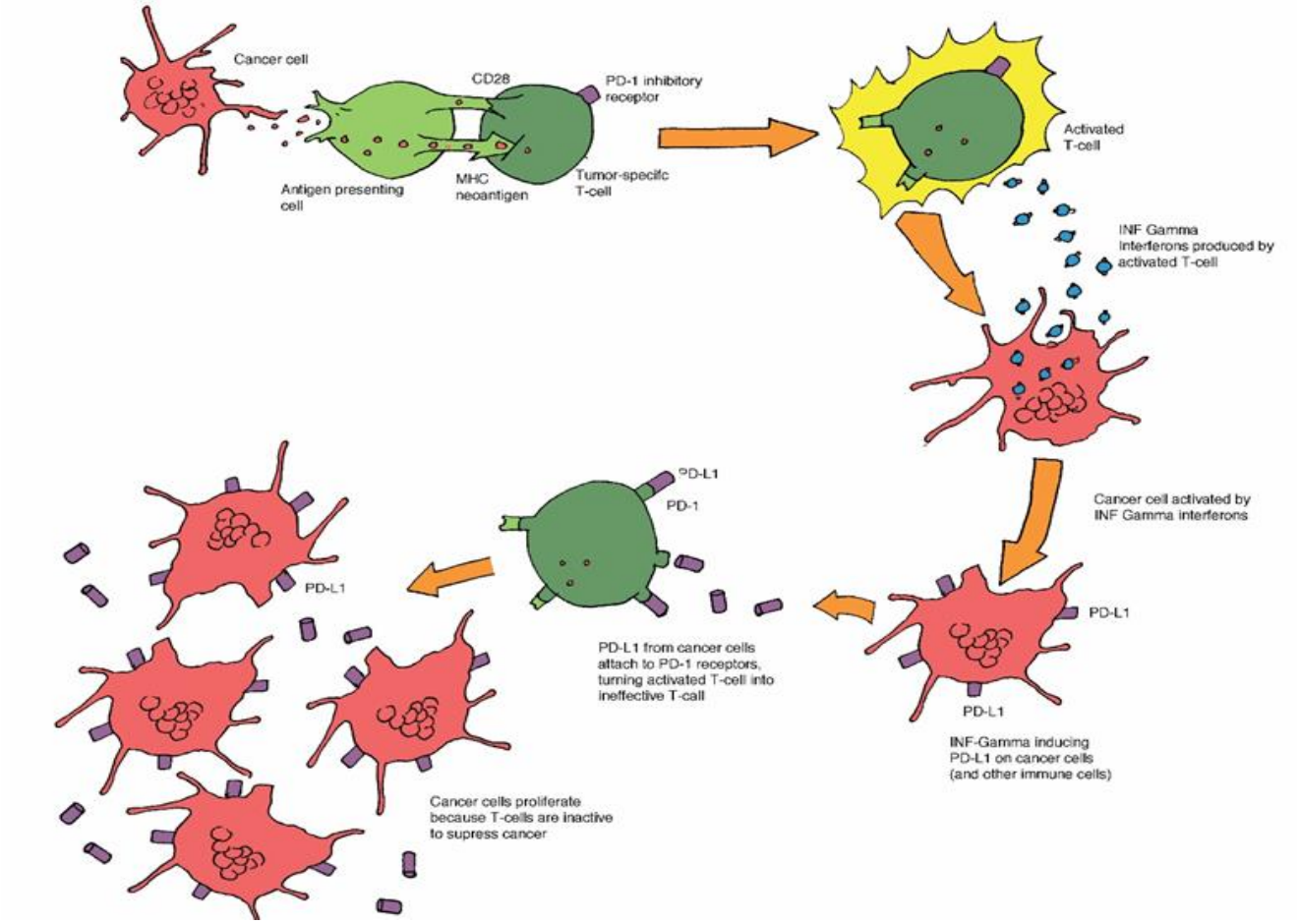


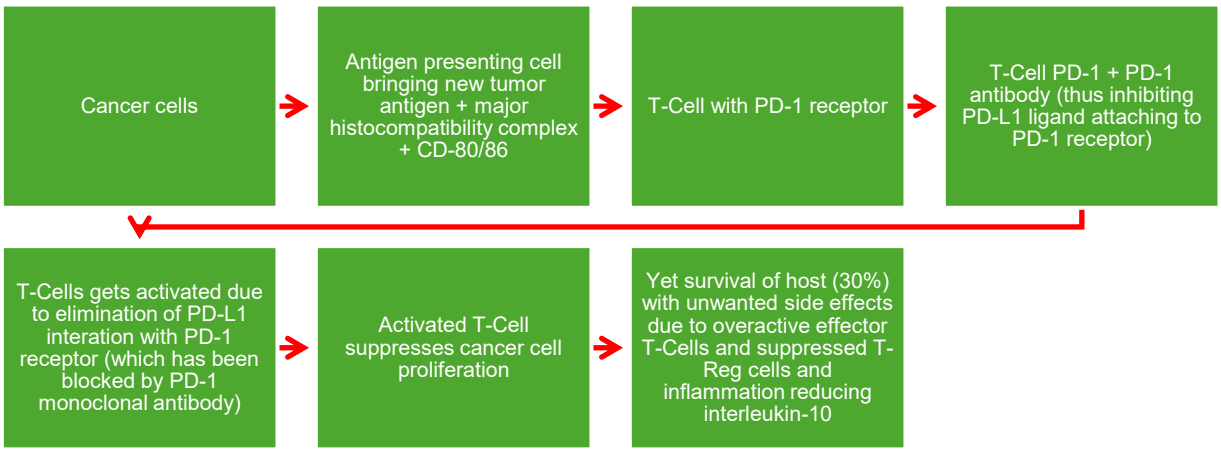
FIGURE 22: A detailed pictorial presentation illustrating the specific role and mechanism for PD-1 as a negative regulator of T-Cell response to allow cancer cells to proliferate in a tumor.



The **PD-1/PD-L1 blockade**—using specific monoclonal antibodies against the PD-1 antigen—can inhibit this immunosuppressive process, thereby allowing T-cells to remain effective. This mechanism forms the theoretical basis of **checkpoint immune therapy** using PD-1/PD-L1 inhibitors, a breakthrough discovery by Nobel Laureate Dr. Tasuku Honjo for cancer treatment.[45,46]

Since checkpoint inhibition therapy is only about 30% effective, combining it with **multiple mixed strain probiotic therapy** could significantly enhance cancer treatment efficacy with minimal side effects. This hypothesis has been experimentally validated through clinical trials. The results of these trials, along with the physiological and molecular mechanisms underlying the success of the combined therapy, are presented in **Figures 23 through 25**. The effect of monoclonal antibody specific to PD-1 enhancing the effect of T-cells through binding to PD-1, thus eliminating the interaction of PD-L1, is presented schematically in **Figure 23**.

FIGURE 23: Schematic diagram showing PD-1 checkpoint inhibition by PD-1 monoclonal antibody to inhibit cancer cells (30% survival but with unwanted side effects).



The improved effect of treating cancer by simultaneously administering multiple mixed-strain probiotics along with PD-1-specific monoclonal antibody is presented schematically in **Figure 24** and pictorially in **Figure 25**. The results clearly proved that probiotic therapy can be used safely as an adjuvant therapy to enhance (by 60%) the immune checkpoint therapy with least side-effects and relapses.[169,172,174,175]

FIGURE 24: A schematic diagram showing PD-1 checkpoint inhibition by PD-1 monoclonal antibody along with Multiple Mixed Strain Probiotic Therapy (adjuvant cancer therapy) to inhibit cancer cells (over 60% survival of cancer patients proven with having the least side effects and cancer relapse).

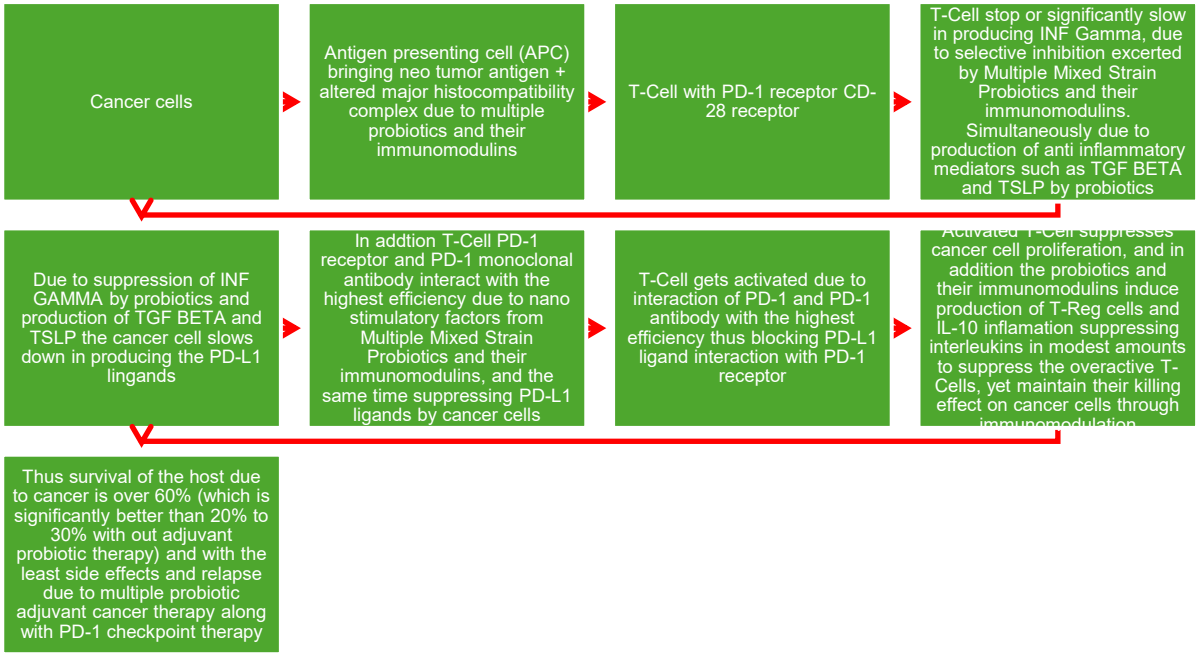


FIGURE 25: A Pictorial Representation of PD-1 Immune Checkpoint Therapy to Treat Cancer and its Unavoidable Autoimmune Side-Effects Which can be Controlled and also Enhance Cancer Therapy Through Multiple Mixed Strain Probiotic Therapy with the Least Side-Effects and Relapse.

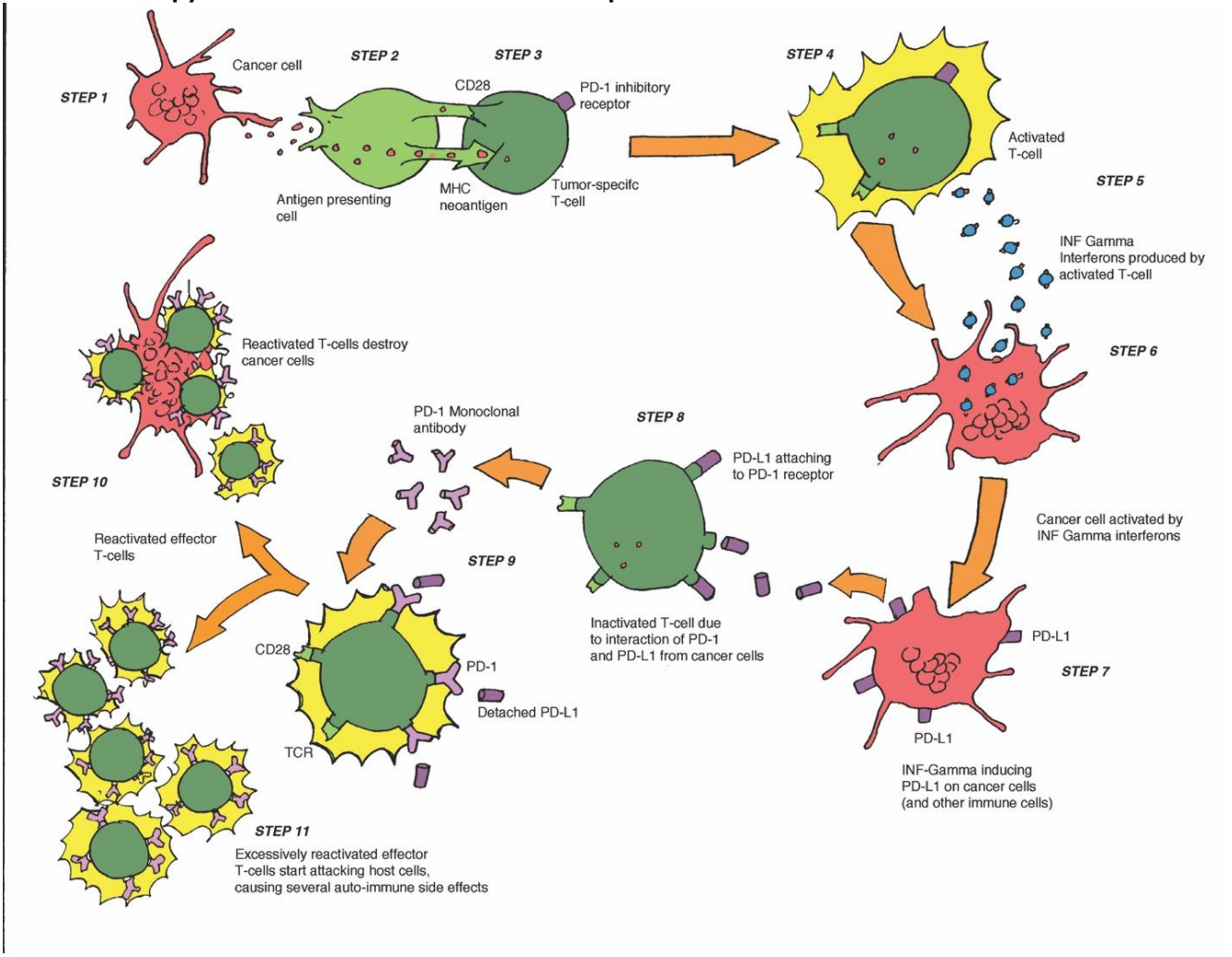


Figure 25 can be best interpreted by going through the details outlined in Fig 24. Probiotics play a significant role at step 4 and 5 of fig 25 by reducing the production of INF-gamma. In step 8, probiotics interfere with the attachments of PD-L1 to PD-1. In step 8, probiotics significantly improve the attachment of PD-1 monoclonal antibodies to PD-1 thus eliminating the PD-L1 interaction. If the probiotics were not included as optional therapy, the result would be as shown in step 11 resulting in severe side effects. However, as shown in step 10 the reactivated T-cell will destroy the cancer cells without inducing side effects under the influence of probiotic immunomodulins through orchestrated immunomodulation.

In addition to PD-1, **CTLA-4** is another immune checkpoint receptor expressed on activated T-cells. When upregulated, CTLA-4 competes with CD28 and exhibits a stronger affinity for CD80/86, the binding of CTLA-4 to CD80/86 inhibits T-cell activation. Tumor cells exploit this pathway to suppress the initiation of immune responses, resulting in decreased T-cell activity.

Antibodies specific to CTLA-4 (by binding to CTLA-4) can restore immune function by enhancing T-cell accumulation, activity, and survival, as well as reducing regulatory T-cells (Tregs). This is the principle behind **CTLA-4 checkpoint inhibition therapy**, discovered by Nobel Laureate Dr. Allison.[47] However, both PD-1 and CTLA-4 checkpoint inhibition therapies are associated with undesirable side effects, such as autoimmunity and excessive inflammation in various organs.

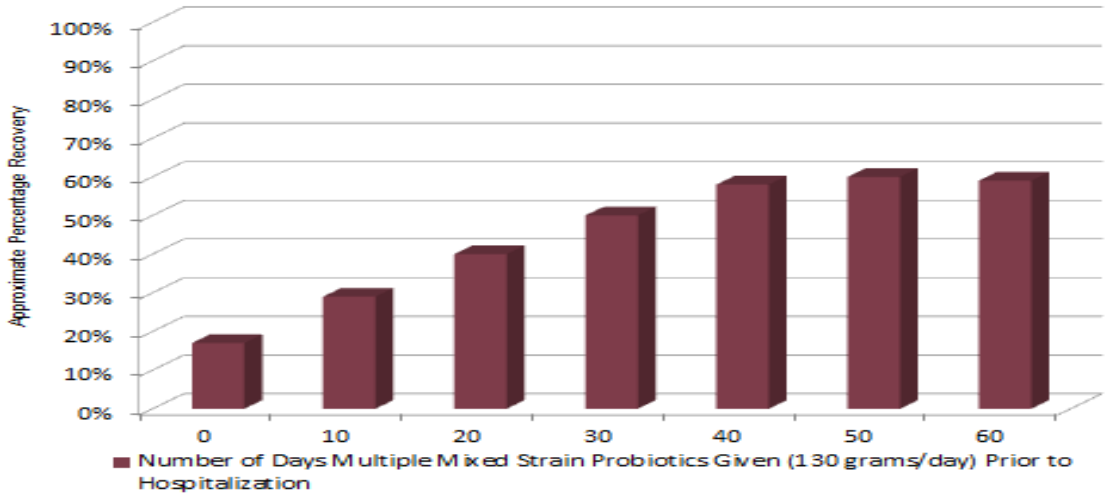
Several researchers have suggested that **gut microflora** may enhance the effectiveness of checkpoint immune therapy, likely due to the immunological interplay between the undefined gut microbiota and the checkpoint therapy.[163] Despite this hypothesis, prior investigations did not specifically focus on this aspect.

These findings collectively highlight the beneficial role of multiple mixed strain probiotics and their immunomodulins in significantly improving the efficacy of both checkpoint inhibition and standard cancer therapies.

The effect of administering multiple mixed strain probiotics for three weeks prior to initiating cancer treatment has been clinically evaluated to determine the percentage improvement in treatment outcomes. The detailed composition of the probiotics and the methodology used in the clinical trials are presented in the author's referenced publication.[169,163]

The results of the clinical trials (of administering probiotics prior to treatment) are shown in **Figure 26**. These results clearly demonstrate that probiotic administration prior to cancer treatment significantly enhanced recovery from cancer. The degree of improvement was directly proportional to the number of days the probiotics were administered. Notably, a significant improvement was observed after 40 days of probiotic use prior to treatment.

FIGURE 26: The results of Defined Multiple Mixed Strain Probiotics administered prior to hospitalization as adjuvant therapy along with the standard cancer therapies on the efficiency of curing cancer.

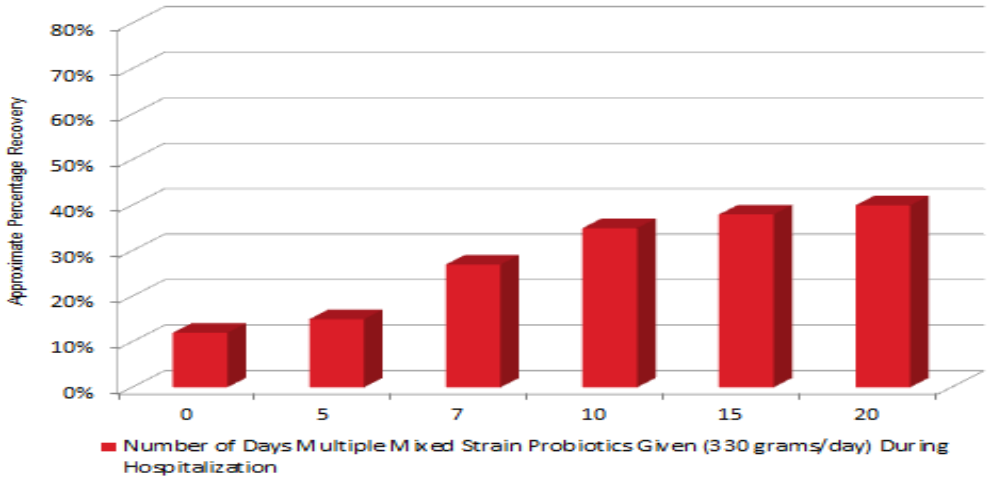


No substantial improvement was noted beyond 40 days of administration, suggesting that the probiotics had already become well established in the intestinal tract. This establishment positively influenced the effectiveness of cancer treatment, likely due to enhanced immune response through beneficial immunomodulation.

The effect of administering the multiple mixed strain probiotics along with the immune check point therapy proved that the cancer treatment efficiency was greatly improved. The results of clinical trials are presented in Fig 27.

Figure 27 illustrates the results of trials investigating the impact of probiotic administration during cancer treatment. Starting from 10 days and continuing up to 20 days, the recovery rate steadily improved. These findings indicate that multiple mixed strain probiotics can be used both as preventive as well as therapeutic adjuvants to enhance the efficacy of cancer treatment.

FIGURE 27: The results of Defined Multiple Mixed Strain Probiotics administered during hospitalization as adjuvant therapies along with the standard cancer therapies on the efficiency of curing the cancer.



Figures 18, 19, 20, 26 and 27 are reproduced from the following article by Dr. Malireddy S Reddy, published in the International Journal of Pharmaceutical Sciences and Nanotechnology (this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy MS. Immunomodulatory effect of "Dr. M.S. Reddy's multiple mixed strain probiotic therapy", to cure or prevent hospital acquired (nosocomial) infections due to Clostridium difficile (C. diff), other pathogenic bacteria and autoimmune diseases. Int J Pharm Sci Nanotech. 2018;11(1):3937-3949. (Reference No. 170)

Figures 22 and 25 are reproduced from the following article by Dr. Malireddy S Reddy, published in the International Journal of Pharmaceutical Sciences and Nanotechnology(this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy MS. Dr. M.S. Reddy's multiple mixed strain probiotics adjuvant cancer therapy, to complement immune check point therapy and other traditional cancer therapies, with least autoimmune side effects through eco-balance of human microbiome. Int J Pharm Sci Nanotech. 2018;11(6):4295-4317. (Reference No. 169)

Net effect, the cancer treatment efficiency can be greatly improved through the elimination of dysbiosis either prior to cancer treatment or during cancer treatment using multiple mixed strain probiotics along with their immunomodulins with least unwanted side effects and also with least relapse. This aspect of adjuvant therapy along with the traditional cancer therapies must be seriously undertaken to protect people from cancer deaths in the future. The results of this investigation proved that probiotic therapy can be used both as a preventive or clinical adjuvant therapy. The selection of individual probiotic strains on the basis of their immunomodulins (including bacteriocins) must be carefully viewed prior to making a multiple mixed strain probiotic blend to be used as an adjuvant cancer therapeutic agent. A list of bacteriocins and other immunomodulins produced by several probiotic strains are presented in the following section of this article.

13) PREVENTION OF VARIOUS DISEASES THROUGH PROBIOTIC SELECTION

This section explores the selection of probiotic strains (by specific genus and species) to prevent/ assist in the treatment of various diseases and syndromes as primary therapeutic agents or adjuvants alongside other medications or treatments.

Previously, I outlined the well-documented physiological and therapeutic properties of individual probiotic strains.[6-32] Several physicians, dietitians, and nutritionists have asked me about the appropriate selection of probiotic strains to recommend to patients. In response, I have compiled a list of multiple probiotic strains that can be effectively used either to prevent or treat specific medical conditions.

The selection and pairing of probiotic strains are based not only on their physiological and therapeutic benefits but also on their immunomodulatory properties. **Table 6** presents various bacteriocins and immunomodulins produced by specific probiotic strains that were used in this study.

TABLE 6: List of Bacteriocins, Immunomodulins and Bioactive Peptides Produced by Individual Strains of Probiotic Bacteria used as Therapeutic Aids – Used in this Study - to Assist to Prevent or Cure Several Diseases or Syndromes.

Probiotic Culture	Bacteriocins Produced by Probiotic cultures	Other Immunomodulins besides bacteriocins
Streptococcus thermophilus	Thermophilin 110, 347, 13	Lactic acid + Acetaldehyde + Formic acid
Lactobacillus bulgaricus	Bulgaracin BB18	Lactic acid + bio pepdites + short chain fatty acids, Acetic, Butyric and Propionic acids + expolysaccharides
Lactococcus lactis var lactis	Nisin, Lacticin, Lactococcin	Lactic acid + Hydrogen Peroxide, Gamma-aminobutyic acid
Lactococcus lactis var cremoris	Diplococcin, Lactococcin G	Lactic acid + dipeptides, etc.
Lactococcus lactis var lactis subsp diacetylactis	Nisin-Z, Lactolisterin BU, Bactericin S50	Diacetyl + Acetyl Methyl Carbinol + Lactic acid
Pediococcus acidolactici	Pediocin PA-1	Gamma Amino Butyric Acid (GABA) and other organic acids
Lactobacillus helveticus	Helveticin-J, Lactocin 27 Helveticin-V1829, Bacteriocin PJ4	Lactic acid + Acetic acid, and Bioactive peptides, etc.
Lactobacillus acidophilus	Acidophilin, Lactacin B	Lactic acid + hydrogen peroxide
Propionibacterium shermanii	Propionicin, SM1 and SM2, T1, F Jensiniin P	Propionic acid, Acetic and Butyric acids, Beta-glucan polysaccharide
Propionibacterium jensenii	Jenseniin G, Propionicin SM1	Propionic acid, Acetic and Butyric acids, protease-activated anti-microbial peptide
Streptococcus faecium	Enterocin A, P, Q, RT-11	Acetic acid and Lactic acid, etc..
Brevibacterium linens	Linocin M18, Linenscin A, Linencin OC2	Acetic acid, Isovaleric acid, Caproic acic, Acetone, etc..
Lactobacillus plantarum	Plantaricin A, S and LPL-1	Pyroglutamic dipeptides including Pyro-phenylalanine and Pyro-tryptophan
Bifidobacterium bifidium	Bifidocin B	Acetic acid, Lactic acid, Formic acid, butyric acid
Bifidobacterium longum	Bifidin 1, Bisin, Bifidococcin-664	Acetic acic, Lactic acid, Formic acid and succinate
Lactobacillus sporogenes	Coagulin	Antimicrobial peptides, Lactic acid, Butyric acid
Lactobacillus casei	Caseicin 80, Lin 333, Caseicin TN-2	Lactic acid, acetate and acetoin
Lactobacillus rhamnosus	Lactocin 160, Rhamnosin A, Bacteriocin 1.0320, GP1, XN2, BFM216 RC 20975, CLk-01, etc.	Short chain fatty acids such as acetate, butyrate and propionate, extracellular polysaccharides, proteins P40, P75
Lactobacillus reuteri	Reuterin, Reutericyclin, Reutericin	Organic acids, Ethanol, Lactate, Acetate

TABLE 7: Probiotic Strains that may be Used Individually or in Combination (as Multiple-Strain Blends) with Notable Therapeutic Effects to Prevent or Support the Treatment of Obesity, Blood Sugar Imbalance, High Cholesterol, Hypertension, Allergies, Viral Infections, Arthritis, and Cancer.

Obesity and Blood Sugar	High Cholesterol	Hypertension	Allergies	Viral infections	Arthritis	Cancer
**L. plantarum*	*Sacchromyces boulardi* *Penicillium roquefortii* *Penicillium camembertii* *Brevibacterium linens* *Lactococcus lactis subsp. lactis* *L. bulgaricus*	*L. plantarum* *Lactococcus lactis subsp. lactis* *L. helveticus*	*Lactococcus lactis subsp. cremoris* *L. plantarum* *L. acidophilus* *Streptococcus thermophilus*	*L. plantarum* *L. rhamnosus* *L. casei* *L. bulgaricus* *L. sporogenes* *Lactococcus lactis subsp. lactis*	*L. acidophilus* *L. helveticus* *L. casei*	*L. plantarum* *Lactococcus lactis subsp. lactis* *Propionibaterium shermanii* *Propionibacterium arabinosum* *Penicillium roquefortii* *Sacchromyces boulardi* *Brevibacterium linens*

* L stands for genera *Lactobacillus*

TABLE 8: Selected probiotic strains to prevent or treat lactose intolerance, Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), sleep apnea, anxiety and depression, antibiotic-associated diarrhea, fungal infections, immunosenescence in the elderly, and poor immune responses to vaccines.

Lactose intolerance IBS, IBD	Sleep apnea	Anxiety-depression	Antibiotic associated diarrhea	Fungal infections	Immune-senecence	Sluggish response of vaccination
**L. plantarum*	*L. helveticus*	*Lactococcus lactis subsp. cremoris*	*L. acidophilus*	*Propioni-bacterium shermanii*	*L. casei*	*Lactobacillus rhamnosus*
L. paraceasei	*L. acidophilus*	*L. acidophilus*	*Streptococcus thermophilus*	*Propioni-bacterium arabinosum*	*L. helveticus*	*Lactobacillus sporogenes*
Bifidodacterium bifidum		*L. plantarum*	*L. plantarum*	*Lactococcus lactis subsp. lactis var diacetylactis*	*L. acidophilus*	
Bifidobacterium longum		*L. helveticus*	*L. rhamnosus*	*L. acidophilus*	*L. bulgaricus*	
L. acidophilus					*Sacchrumyces boulardi*	
L. sporogenes					*Lactococcus lactis subsp. lactis*	
Streptococcus faecium						
Sacchrumyces boulardi						
Streptococcus thermophilus						

*L. stands for genera Lactobacillus

Tables 7 and 8 are reproduced from the following article by Dr. Malireddy S Reddy, published in the JAAPI Journal (this is an open-access article distributed under the terms of the Creative Commons Attribute License); Reddy MS. Probiotics: genesis, current definition, and proven therapeutic properties. JAAPI. 2021;1(2):18-26.(Reference No. 167)

In addition to the combinations listed above, a skilled physician or microbiologist with clinical experience can develop custom probiotic blends tailored to the patient's specific condition and the nature of the disease, whether for prevention or as an adjunct to other therapies.

Conclusion

This article has outlined the significant role of probiotics as both preventive and clinical therapeutic agents in the management and treatment of multiple diseases. To make the content clearer and easier to follow, several detailed figures and tables have been included. Major emphasis has been placed on the fundamentals of probiotics, including their morphology, cell physiology, and their distribution and predilection sites in the gastrointestinal tract. In addition, a thorough explanation of cytokines, interleukins, chemokines, and interferons is provided so that readers without a strong background in immunology can follow the concepts without confusion. The therapeutic properties of several probiotic strains are also listed, enabling physicians to select the strains most appropriate for treating specific ailments or syndromes.

The therapeutic effects of multiple mixed-strain probiotics in treating various diseases are discussed in detail, including the pathophysiology of each condition and the physiological mechanisms underlying the curative effects of probiotics. The diseases addressed include cytokine storm during COVID-19 infection; intestinal infections (including *Helicobacter pylori* infection); lactose intolerance; diabetes; hypertension; obesity; allergies; anti-aging; hospital-acquired infections; and cancer. Of these, the greatest emphasis is placed on COVID-19, hospital-acquired infections, and cancer, as these are associated with the highest morbidity and mortality rates. Supported by clinical trial data, this article provides molecular-level explanations of how probiotics can prevent or treat these conditions. The therapeutic effects of probiotics on diabetes, hypertension, obesity, anti-aging, and allergies are also discussed, though in less detail due to space limitations.

This research and review article is the first of its kind to highlight the wide range of therapeutic functions of individual probiotic strains within a multiple mixed-strain probiotic blend, as applicable to both preventive and clinical medicine to curb the diseases. COVID-19 has infected over 700 million people worldwide, with more than seven million confirmed deaths. This article explains the pathophysiology of COVID-19 and the control mechanisms exerted by multiple mixed-strain probiotics, including their immunomodulatory effects. Such information is of great significance for controlling future unforeseen viral or bacterial pandemics to protect humanity.

Hospital-acquired infections caused by antibiotic-resistant microorganisms such as C. diff (*Clostridium difficile*) and MRSA (*Methicillin-resistant Staphylococcus aureus*) have been successfully treated with the aid of probiotics. This is highly significant given projections that such nosocomial infections could claim over 10 million lives annually by the year 2050. Furthermore, clinical trial

data presented in this article demonstrate that several cancer treatments can be significantly enhanced—with fewer side effects and reduced relapse rates—through the use of multiple mixed-strain probiotics and their immunomodulatory components as adjuvants alongside immune checkpoint therapy and other traditional cancer treatments.

Overall, multiple mixed-strain probiotics, along with their immunomodulins, have enormous potential to serve as preventive or therapeutic agents in both preventive and clinical medicine. They may be used either as stand-alone primary therapeutic agents or as adjuvants to enhance established therapies, thereby helping to curb a wide range of diseases.

Disclosure

The author is a scientist with degrees in Veterinary medicine, MS degree in Microbiology, and Ph.D. in Bacteriology, virology and Food Technology from Iowa State University, USA. He has been heavily involved in probiotic research for over 50 years, holds over 150 national and international Patents and has published over 170 research articles. He serves as the president of IMAC Inc. which is involved in the manufacture of food grade beneficial bacterial cultures and other high-tech enzyme-fortified functional products that go into manufacture of various dairy products in the United States, Canada, Europe, Asia, Korea, and South America.

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Conflict of Interest: No conflict of interest.

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