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Review Article

## Probiotics, their Health Benefits and Applications for Development of Human Health: A Review

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### ABSTRACT

Gastrointestinal microbial flora plays a major role in health of host. The person with the healthy digestive system is the indication of proper health. Probiotics bacteria are live nonpathogenic microorganism which has beneficial effects on host gastrointestinal tract which is mentioned in articles viz. Recent Advances in Pharmaceutical Approaches to Colon Specific Drug Delivery. Optimum population of probiotics bacteria are essential for the maintenance and effective functioning of the digestive system. Hence probiotics are the good therapeutic agents for the various abnormal conditions of gastrointestinal tract such as inflammatory bowel disease, chrohn's disease, colon cancer etc. Probiotic micro biota also fights against pathogenic infections of GIT such as *H. pylori* infection by production of some antimicrobial chemical secretions such as bacteriocin. Recent studies and innovations and studies found that the probiotic bacteria are beneficial in the prevention and curative treatment of various disease and disorders like colorectal cancer, infection of urinary tract (UTI), allergic condition, cardiovascular disorders and depressive disorders. Probiotics are administered as nutraceutical products in the form of both conventional pharmaceutical dosage forms and traditional non-conventional food products, inclusion complexes with cyclodextrins effectively, sustained release tablets by solid dispersion technology etc. Probiotics are significantly gaining popularity due their wide application and safety. This paper presents the comprehensive review on the probiotics profile along with its some therapeutic applications, delivery approaches and current aspects.

**Keywords:** Probiotics, mechanisms, Health benefits, cardiovascular disorders, safety, colon targeted drug delivery system.

**Article Info:** Received 11 June 2019; Review Completed 21 July 2019; Accepted 23 July 2019; Available online 15 August 2019



### Cite this article as:

Sanap D, Garje M, Godge G, Probiotics, their Health Benefits and Applications for Development of Human Health: A Review, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):631-640 <http://dx.doi.org/10.22270/jddt.v9i4-s.3231>

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### INTRODUCTION:

Probiotics are living or viable bacteria which act as supplementary microorganisms that exhibit beneficial health effect on the host's health by enhancing its gastrointestinal microbial balance. Healthy life is a dream of every person and healthy digestive system is basically indication of good health. [1, 2, 3]The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) have defined probiotics as, "Live microorganisms, which when administered in adequate amounts confer a health benefits on the host." [4, 5, 6]

The term 'Probiotics' was first applied by Stillwel and Lilly in 1965 to the substance which is produced by one microorganism and that promote the growth of another. Later on 1974, Porker proposed a definition of probiotics as, "organisms and the substances, which contribute to intestinal microbial balance." [7] Each and every microorganism cannot be considered as a probiotics. There are certain criteria's for considering microbial strain as a probiotic. According to WHO/ FAO guidelines regarding to

probiotics, the manufacturer who performs the manufacturing of probiotics, should register their strain with on International Depository. [8]

Effectiveness and activity of probiotics can be enhanced by substances called 'Prebiotics'. These prebiotics act as supplement to the probiotics bacteria. The combination of prebiotics along with probiotics is termed as 'synbiotics'.

The useful and promising strains of probiotics include various members of genera *Bifidobacterium*, *Lactobacillus* and *Enterococcus*. The representatives of above genera are *Lactobacillus acidophilus*, *L. johnsonni*, *L. casei*, *Lactobacillus gasseri*, *L. rhamnosus*, *L. plantarum*. The species of *Bifidobacterium* includes the *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium bifidum*, and *Bifidobacterium infantis*. *Enterococcus* are *E.faecalis* and *E. faecium*. [9, 10, 11, 12]

Probiotics provide variety of benefits. It provide effect on immunological functions, aid in digestion, protect GIT from the infectious bacteria such as *H. pylori*, *E. coli*. Probiotics

are also used to improvement of lactose intolerance, to lower the body cholesterol level, to treat chronic disease, ulcerative colitis, IBS and in antibiotics associated diarrhea. Probiotics also used as a medium or carrier of drug

delivery to the GI tract. Probiotics are delivered in various forms such as food product, deep-freeze form, dairy products, meat etc. [13]

### COMPOSITION OF GUT FLORA:-[13]

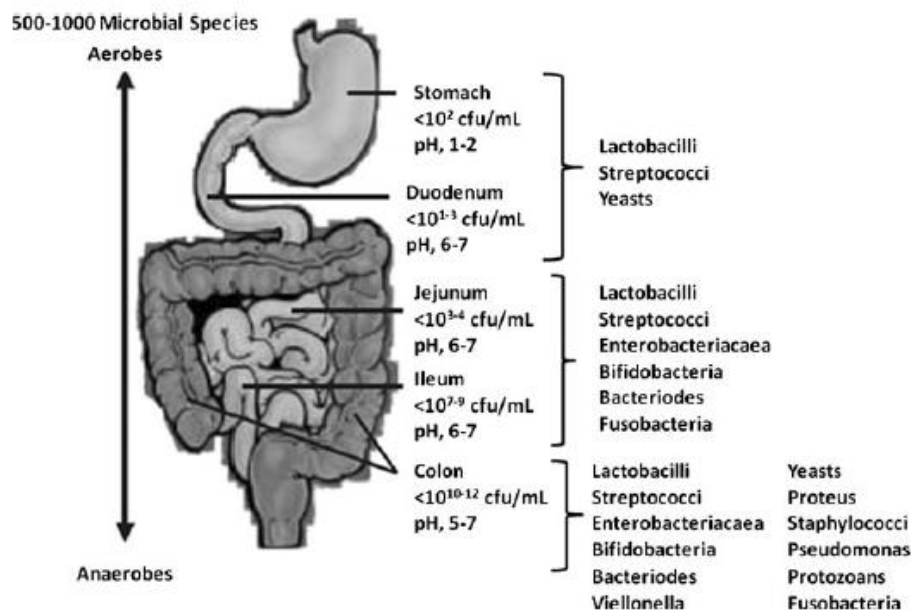


Fig. 1 Detail Composition of Gut Flora

### MECHANISM OF ACTION OF PROBIOTICS:-

Probiotics act by several mechanisms, such as maintenance and enhancement of epithelial barrier, improved adhesion to intestinal mucosa and simultaneous inhibition of adhesion of pathogen, competitive exclusion of pathogenic microbes, generation of anti-microbial substances and immunomodulation action. [14, 15]

Intestinal barrier is major defense mechanism which maintains intestinal integrity and function. Intestinal barrier composed of layer of mucous, peptides having activity against microbes, IgA and epithelial junction adhesion complex. Probiotic bacteria have effect on various component of epithelial barrier by more production of intestine. [16, 17]

Probiotics act by prevention of the colonization of various pathogenic bacteria in gastrointestinal tract (GIT). Probiotics also act by preventing the binding of pathogenic microbes to enterocyte by producing inhibitory components such as Lactic acid, bacteriocin, and toxic metabolites of oxygen. The attachment of probiotics to receptor initiates the signal which results in cytokines production. The Butyric acid synthesis causes increased enterocytes turnover and neutralization of dietary carcinogen. Specific serum IgA

production results in enhanced immune response [9, 18, 19, 20, 21]

By these several mechanisms the probiotics keeps the gastrointestinal tract healthy.

### IDEAL PROPERTIES OF PROBIOTICS:-

1. Resistant to digestion.
2. Highly adherent to the cell of intestinal wall.
3. Stability in gastric acid, bile, oxygen and various enzymes.
4. Ability to produce anti- microbial agents for intestinal tract protection.
5. They should not be pathogenic to body and should be safe.
6. Should have ability to maintain sufficient normal balanced flora.

### COMMERCIAL PROBIOTIC MICROORGANISMS:-[7, 9]

Some commercially marketed formulations of probiotics are given below.

Table .1 Some Commercially Marketed Formulations of Probiotics

Sr.no.	Product name	Comment	Culture of probiotics used
1	Flora Grow (Arise & Shine)	Generate pH between 6.5 and 7. Because essential bacteria in GIT tract start to die off.	<i>Bifidobacterium infantis</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium bifidum</i>
2	Bioflorin (CerbiosPharma)	Used for the prophylaxis and treatment of intestinal diseases	<i>Enterococcus</i> LAB SF 68
3	Subalin		Recombinant <i>Bacillus subtilis</i>
4	SWELTY® Gastro Protect (Nestle)	It protect the stomach from <i>H. pylori</i> infection and controls stomach discomfort	<i>Lactobacillus johnsonii</i> La 1
5	Kyo-Dophilus tablets (Wakanaga Probiotics)	This is a stable formulation. Refrigeration is not essential. It is chewable, sugar free , tasty and is completely vegetarian	<i>Lactobacillus acidophilus</i>
6	Align (Procter y Gamble)	Available as capsule form and daily single dose keep digestive system healthy with healthy bacteria.	<i>Bifidobacterium infantis</i> 35624
7.	Bifa 15 (Eden Foods)	The bacterial strain is encapsulated so as to bypass the stomach acidic environment and reaches to the colon	<i>Bifidobacterium longum</i>
8	URO VAXAM ® (Apsen)	Used in immunotherapy and protect lower urinary tract	<i>Escherchia coli</i>
9.	Kyo-Dophilus capsules	Each capsule contains about 1.5 billion live bacterial strain cells.	<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium longum</i>
10	Activia® Yogurt (Danone)	It helps in regulation of digestion function of digestive system	<i>L. bulgaricus</i> , <i>S. thermophilus</i>
11	Mutaflor (Ardeypharm)	It is beneficial in IBS and functional bowel disease.	<i>Escherschia coli nissle</i> 1917
12.	TH1 Probiotics (Jarrow formulas)	It contain heat treated strains so they are safe in case of persons having leaky gut and is severely immune compromised.	<i>Bifidobacterium longum</i> , <i>Saccharomyces boulardi</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus plantarum</i> .

### APPLICATIONS/ THERAPEUTIC USES:-

Many diseases and abnormal physiological conditions are treated with use of probiotics. On the basis of animal studies, preliminary human models study, uncontrolled studies such numerous studies provide encouraging evidence that specific strains of probiotics are beneficial in the preventing and treating the various diseases and conditions. The probiotics have various potential benefits including improved nutrition, growth and prevention & treatment of various gastrointestinal disorders. The various therapeutic uses of probiotics are briefly described as follows- [6, 22, 21]

#### 1. Cancer

Currently in the world cancer is one of the major cause of death of humans. Among them near about 75% of cancer suffered patients dies which are related to their diet and lifestyle, where about 50% of these deaths are associated with diets. (World Cancer Research Fund, 1997). Colon Cancer or colorectal cancer is the most prevalent form of cancer, which are specially associated with human habits of diet. According to certain animal studies and some in vitro studies shows that the intestinal or gut microbial flora may exhibit anticancer activity. But fact is that study is limited only up to in vitro testing. Animal and clinical trials are still not performed. They decreases risk associated with the diet. So, probiotics may serve as a beneficial role in the colon cancer and superficial bladder cancer. [7, 23] The pathological imbalance in the gastrointestinal microbial community is observed in the affected subjects as compared to the normal subjects. In the case of colorectal cancer, many potential pathogen such as *Pseudomonas*, *Acinetobacter* and *Helicobacter* and decreased level of the beneficial bacteria,

like butyrate producing bacteria are observed. Due to this imbalance between the pathogenic bacteria and beneficial bacteria, this condition promotes implementation and tumorigenesis in colon which directly leads to colorectal cancer. [24]

There are many in vitro experiments are undergoing to demonstrate the cytotoxic effect of some lactic acid bacteria (LAB) strains in cancerous cells. The probiotic may be useful in malignant tumor but not in benign tumour. They act by various mechanisms. The probiotics get agglomerated in malignant tumour cells and this agglomeration is less in organ such as spleen and liver. [13] Probiotic act by increased synthesis of the cytokines such as Interleukins (IL-2 and IL-12), some antioxidants (SOD, GSH, CAT) and Anti-angiogenic factors. They also reduce damage to DNA, many carcinogenic enzymes, proteins which are specific to carcinogenicity and size of tumour. Various metabolites of probiotic bacteria have suppression action colon cancer development. It includes SCFAS, Acetate, propionates, butyrates. From the experimental study it is found that butyrate exhibit anti-tumour effect by inducing apoptosis, preventing proliferation, certain changes in expression pattern of gene and modulation of cytokines. In vitro study of *Lactobacillus fermentum* NCIMB-5221 and NCIMB-8829 showed action on colorectal malignant cells by promoting normal epithelial colon cell growth due to the production of SCFA's i.e. ferulic acid. Other species of probiotic strains like *Lactobacillus acidophilus* LA102 and *L. casei* LC232 showed a significant cytotoxic activity and proliferative activity against 2 colorectal cell lines. So the dietary control may play major role in controlling and management of cancer. Probiotic delivery which modulate the gastrointestinal microbial

community is become great approach and have good potential to prophylaxis and treatment of cancer. [25, 26, 27, 28]

Strains used:-*L. acidophilus*, *L. caseishirota* strains and *Lactobacillus GG*

## 2. Gastrointestinal application<sup>[29]</sup>

Probiotics are very beneficial in preventing and treating of GIT related diseases and disorders. There are some probiotics which prevents diverse intestinal diarrhoea inducing disorders like lactose indigestion. Some are responsible for the treatment and prophylaxis of gastrointestinal and urogenital infections. Banerjee I, Pal K and Babu N et.al. Formulated emulsion gel as carrier based probiotics formulation for gastrointestinal conditions like diarrhea, chrohn's disease and ulcerative colitis. [30] Probiotics are able to inhibit the mutagenicity of gastrointestinal contents and reduces the incidences of gastrointestinal tumors. Some useful traits of the probiotics responsible for the illustration of bile tolerance, acid resistance and attachment to the epithelial tissue of host to show the action as antagonist for pathogenic microorganisms. [4] Probiotics species like *L. plantanum* generally used to cure flatulence and abdominal pain; *L. GG*, *L. reutri* and *S. boulardii* generally cures overall conditions of GI tract. GI disorders like diarrhea, paining, bloating can be treated with *S. boulardii*. [31] Mateescu MA, Calinescu C developed chitosan self-stabilized matrix based colon targeted probiotics formulation. [32]

## 3. Antipathogenic activity<sup>[33,34]</sup>

One of the important and useful effect of probiotics is antipathogenicity. Probiotics are used to inhibition of the growth of pathogenic bacteria by the production of SCFA's (short chain fatty acids) which maintains the pH of the colonic lumen at the appropriate conditions. As the probiotic bacteria are non-pathogenic bacteria they have ability to inhibit pathogenic bacteria and protect the body. Some of the probiotics produces compounds like bacteriocin, ethanol, organic acid, diacetyl, acetaldehydes, hydrogen peroxides and peptides which have anti-pathogenic action. Anti-pathogenic compounds like bacteriocin and peptides increases the membrane permeability of target cells which causes depolarization of cell membrane potential and which finally leads cell death. Some of the probiotics activates anti-pathogenic defense pathways in the host. [35]

## 4. Care of UTI<sup>[15, 35, 36]</sup>

Infection of urinary tract by various pathogens and bacteria is termed as 'Urinary Tract Infection' (UTI). It is most commonly prevailing problem often seen in young as well as elder women's. Bacterial infection is the major cause of UTI. Many UTI occurs due to the imbalance vaginal microbial flora. The affected site can be either lower urinary tract or upper urinary tract. Upper urinary tract involves the ureters and kidneys. If infection is limited to the urethra and urinary bladder then it is called lower urinary tract infection. When bacteria enter into the urinary tract and start to grow it lead the infection at that site. So lactic acid producing bacteria are suggested for UTI from many years. In 1973, lactobacilli were observed in vagina of women having no history of urinary tract infection. Many of the medicines fail to cure the UTI's because of resistance to the medicines. So to cure the UTI's there are 50 probiotics species which normalize the microbial flora of vagina. Out of 50 species, *Lactobacillus* species highly influences the microbial environment of vagina. *Lactobacillus* species like *Lactobacillus brevis*, *L. casei*, *L. vaginalis*, *L. salivarius*, *L. reuteri*, *L. delbrueckii* and, *L. rhamnosus* mainly effects on vagina in the conditions of the

bacterial vaginosis (BV) and infection of urinary tract (UTI). Different UTI's can be cured by using above species through the supplement of probiotics. The different species can be administered through vaginal suppositories to cure the urinary tract infections with minimum side effects. Despite there are sufficient clinical evidences demonstrating the effective use of probiotics on urogenital and urinary tract health still there is no sufficient data available to the regular use of such microbiota in urological disorders. Because very less number of trails performed on minimum human subjects.

## 5. Probiotics against diabetes

Generally, probiotics used to enhance the microbial flora in GIT of human body to neutralize any disorder. Probiotics are given with supplementation for proper treatment of any disease or disorder Type-2 diabetes shows significant reduction in the gram +ve firmicutes species. Type-2 diabetes can be treated with the help of probiotics by modulation of gut hormones like gastric inhibitory polypeptide along with glucagon like peptides. Hormone control glucose homeostasis which in turn neutralizes the type-2 diabetes produced due to peripheral insulin resistance. Failure of  $\beta$ - cells in producing insulin can also be treated with the help of probiotics. New probiotics like arabinoxylan and arabinoxylan oligosaccharides resists metabolic disorders by reducing the growth of adipocyte tissues. Prakash S & Lomis L studied the combination of three different metabolically active probiotic strains, Lf5221, Lp8826 and Bi702255 and they concluded that this combination effectively recovered all aspects of diet induced diabetes as well as obesity. If we added some prebiotics along with probiotics we get more prominent results. [14, 33, 37]

## 6. Probiotics against obesity

Obesity can be characterized by some factors like increase in energy availability, abnormality in energy uptake and expenditure, sedentariness etc. Some probiotics have physiological function that regulates body weight. Probiotics strains like *Lactobacillus gasseri* BNR17 inhibit the growth of an adipocyte tissue which contains leptin and adiponectin responsible for obesity. Other strains of probiotics viz; *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium longum* possess hypocholesterolemic effects. Generally probiotics facilitates weight loss by thermogenic as well as lipolytic response via stimulation of adrenergic nervous system. [35, 37, 38] Probiotics species like *Lactobacillus reuteri* CRL1098 decreases cholesterol level in hypercholesterolemic conditions. It also reduces level of triglycerides and the ratio of high density lipoprotein (HDL) to low density lipoprotein (LDL) without any translocation of microbial flora. [9]

## 7. Probiotics against inflammatory diseases

Inflammatory diseases of GIT like Chrohn's disease (CD) and ulcerative colitis (UC) can also be treated with the help of probiotics. Generally, CD may causes inflammation of any part of GIT or may spread to the whole GIT. Both aerobic and anaerobic bacteria contribute to the inflammatory action on GIT. While ulcerative colitis (UC) causes inflammation only to the large bowel. Inflammation may cause to the mucosal, sub mucosal or serosal level. Inflammation can caused with the supplements of probiotics, prebiotics and synbiotics. Combination of Chrohn's disease with the ulcerative colitis known as the inflammatory bowel disease. The certain genes like mutant of the NOD2/CARD15 on chromosome 16 are associated with the chrohn's disease. IBD is characterized with abnormal production of the short chain fatty acid



(SCFA's). SCFA's are important to maintain colonic homeostasis and have an anti-inflammatory effect. But the abnormality in SCFA's produces IBD. Indigestible carbohydrates and fiber as a single component or in combination with probiotic supplement normalize the production of SCFA's. Generally strains of *Lactobacillus*, *Bifidobacillus*, *E. coli* and *Enterobacter* are widely used to treat inflammation. Some genetically engineered probiotics traits produces immune-modulators like interleukin-10, trefoil factors, which help to improve immune system of host. [39, 40, 41]

### 8. Probiotics against allergy

Recent advanced study on probiotics showed an anti-allergy effect of probiotics. In vitro study of strains of *Lactobacillus plantarum* L67 & 06CC2 showed significant results to alleviate allergy symptoms. Allergy associated with disease and disorders treated using *Lactobacillus plantarum* L67 which produces interleukin-12 & interferon- $\gamma$  in host system. *L. plantarum* 06CC2 alleviates all the symptoms of allergy & decreases level of immunoglobulin E and histamine. In case of *L. plantarum* 06CC2 showed that increase in secretion of interferon- $\gamma$  & interleukin-4 in the spleen cells of mice and they are responsible for the prevention of allergic symptoms. [9, 30, 42]

### 9. Probiotics and angiogenesis

Angiogenesis is one of the important process or phenomenon in which new vessel generated from pre-existing blood vessels. It is also useful in wound healing process. Improper angiogenesis leads to the chronic disorder such as cancer, IBD with CD and UC, diabetic retinopathy. A probiotics are found to be beneficial in the heart conditions like coronary heart disease, and notably act on risk factors associated with heart diseases such as cholesterol and TAG. A probiotic strain *S. boulardii* protect host body against intestinal injury & inflammation. *S. boulardii* is a non-pathogenic yeast species. Molecular mechanism behind the action of probiotics not been clear. But it may be act by decrease in visceral hypersensitivity, altering inflammatory cytokine profiles, increase in epithelial barrier function, down regulation of pro-inflammatory cascade etc. [35, 43, 44]

### 10. Probiotics and CNS

In recent years, some studies carried out to see the effect of gut microbiota on brain and CNS. Many clinical trials showed positive results for effect of microbial flora in gut on the brain and CNS. Daily dose of *L. plantarum* WCFS1 showed improvement in the children having autism. *Lactobacillus helveticus* R0052 & R0175 lowers down the psychological distress. Anxiety symptoms in chronic fatigue syndrome can be reduced by *L. casei*. Probiotic strain. *L. rhamnosus* also

used to prevent symptoms in autism spectrum & attention deficit/ hyperactivity disorder. Some gut bacteria produces neuroactive compounds which are similar to the compounds present in host brain. Study on *L. brevis* DPC6108 & *Bifidobacterium dentium* shown that they produce a brain neurotransmitter  $\gamma$ -amino butyric acid (GABA) in large quantity. GABA helps to suppress the anxiety and depression. Combinations of different strains of probiotics can be able to recover the cognitive reactivity of victim to the sad mood. CNS and brain disorders can be cured with the help of species viz; *B.lactis* W, *L. acidophilus* W37, *lactococcuslactis* W19 & W58, *L. salivarius* W2, *L. casei* W5, *Bifidobacterium bifidum*, *L. brevis* W etc. Administration of *L. acidophilus* through oral route regulates mood of people towards rewards and their addictive behavior. [35, 45, 46]

### 11. Probiotics for immunologic enhancement

The person having strong immune system is basic indication of the healthier person. There are different component which modulate host immune system. Interleukins, prostaglandin E production, TNF, gamma interferon, serum protein, albumin, and globulin are some intrinsic component of body that have effect on host immunity. There are several studies reported that probiotics like lactobacilli can be used to enhance the immune system of host. They have ability to modulate the immunological response. The probiotics like *Lactobacillus rhamnosus* GG causes the proliferation of murine T and B lymphocytes and shows the immunomodulatory effects. Their actions are specific dose dependant and duration dependant. *Bifidobacterium breve* YIT4064. When administered orally it causes the activation of human immune system by increasing production of anti-rotavirus IgA or production of anti-influenza virus IgG. Hence *Bifidobacterium breve* YIT4064 protect the host against influenza virus infection and rotavirus infection. Some probiotic bacteria act on proliferation of cell, production of nitric acid and cytokine. Such probiotics are heat killed strains, cytoplasmic extracts including cell wall of *Lactobacillus acidophilus*, *L.gasseri*, *Lactobacillus bulgaricus*, *Lactobacillus reuteri*, *Lactobacillus casei*, *Lactobacillus helveticus* and *Streptococcus thermophilus*. Cell wall as well as cytoplasmic fraction of extract of probiotics produces essential amount of certain immunological factors such as IL-6 (interleukin-6), tumournecrosis factor- $\alpha$  and nitric oxide (NO). From these studies it is observed that lactic acid bacteria have power to stimulate the macrophages & may stimulate other immune cells which produces the nitric oxide (NO) and cytokines. Cytoplasm and also cell wall of probiotic bacteria have such capabilities. There are various different mechanism and actions are observed on different animals such as rats and mice. They stimulate helper T cells (Type 1), decreases the immunoglobulin E (IgE) production and decreases the chances of tumors. [24, 62]

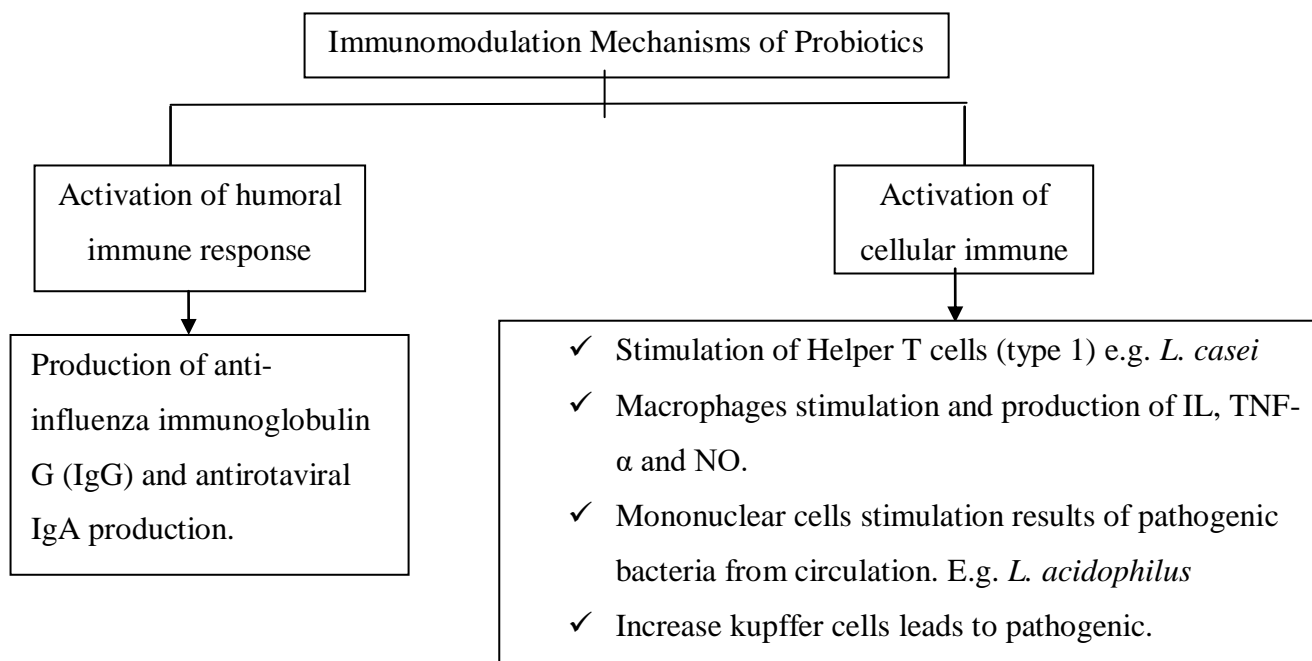


Fig. 2. Immunomodulation Mechanisms of Probiotics

## 12. Probiotic and Respiratory diseases.<sup>[7]</sup>

The probiotics used as preventive agent in certain respiratory tract diseases. Due to the capability of probiotics to exhibit different actions such as immunomodulation, production of substances having antimicrobial activity, probiotics directly shows their action on the pathogenic microorganism. Hence different strains of bacteria can be used in respiratory tract disorders. The respiratory tract disorders include pharyngitis, bronchitis, rhino sinusitis, sinusitis, otitis etc. The various species are employed either single or in combination with other. Administration of the *Lactobacillus rhamnosus* GG in patients having cystic fibrosis decreases exasperated episodes of pneumonia significantly. Probiotic bacteria such as *Lactobacillus rhamnosus* and *L. plantarum* are used to prevent nosocomial pneumonia. In the nosocomial pneumonia pathogenic bacteria *Pseudomonas aeruginosa* are colonized in respiratory tract. Other species used to reduce episodes of respiratory disease are *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus fermentum* VRI-003, *Bifidobacterium longum* SP 07/3, *Bifidobacterium breve* 99.

## 13. Probiotics in cardiovascular diseases<sup>[44, 47, 48]</sup>

Cardiovascular abnormalities and complications are one of the major reason of deaths in the recent some decades. Amongst the various reasons, the diet and food habit is one of the most influencing factor for the development of cardiovascular complications. Hence the functional foods gaining the great popularity and acceptance. These are the nutritionally enriched products that provide health benefits along with the basic nutritional purpose. As said earlier the increased number of deaths occurs due the cases of different form of cardiovascular diseases. As the food have direct impact on health it is essential controlling and examination of dietary pattern and food habits for the minimizing the risk of development of coronary heart diseases. For e.g. Resveratrol which are present in red wine have an antioxidant property and it decrease the cardiac fibrosis. In this condition fibroblast are over activated in heart which results into production of collagen. Elevated level of

produced collagen causes stiffening of heart muscle. Due to stiffened muscle heart loses its efficiency of bold pumping.

Cholesterol level in body is also directly depending upon the diet. The food with high fat and cholesterol content lead to overweight i.e. obesity. Obese patients are at the high risk of cardiovascular diseases. Probiotics doesn't have direct action on heart but still it reduces the incidences of cardiac complications. The probiotic bacteria have action on fat deposition mechanism hence the probiotic bacteria decreases the deposition of fat which lowers the risk cardiovascular disease. In vitro study shows that some strains of *Lactobacillus* such as *Lactobacillus helveticus*, *Saccharomyces cerevisiae*, *Lactobacillus helveticus* CP790 have ability to produce bioactive peptides. These peptides inhibit the activity of Angiotensin Converting Enzyme (ACE). This enzyme play major role in hypertension. Hence probiotics alleviate the hypertensive crises. Probiotic also protect heart from foodborne pathogenic microorganism hence provide protection against carditis. By these different actions probiotic can provide protection to heart from different risk factor.

## PROBIOTICS DELIVERY MECHANISMS

Various approaches are used for the effective delivery of the probiotic bacteria to the gastrointestinal tract including various non-conventional product and conventional pharmaceutical dosage forms. Various non-conventional products are food based commercial products such as cheeses, chocolates, yogurts, creams, milk etc. Conventional pharmaceutical formulations include the different pharmaceutical dosage forms. Vishwakarma N, Ganeshpurkar A et.al. developed and formulated Mesalazine probiotics loaded pectin beads as a novel promising strategy for UC. The probiotics are delivered as Polysaccharide based hydrogel as promising probiotics drug delivery system. Some bacterial strains are delivered as modified emulsion based gel as carrier using natural gums. Mateescu MA, Calinescu C developed chitosan self-stabilized matrix based colon targeted probiotics delivery system formulation. This formulation maintain the viability of the probiotic bacteria

and also protect the bacteria strain from surrounding condition and maintain the stability. The probiotics itself can be used as the carrier for the carrying the vaccines and immunological products. Engineered probiotics are also novel way to effective localization and delivery of the probiotics. Okonogi S, Klayraung S et.al. has developed probiotics containing tablets using the *Lactobacillus fermentum* 2311 as bacterial culture using polymers such as hydroxypropyl methyl cellulose. Chong-suchoet.al. prepared microcapsule for the oral delivery of probiotics expressing M cells homing peptide conjugate BmpB vaccine by encapsulating it into microcapsules by the microencapsulation process. Witzler J.J.P, Pinto R.A. et.al. developed a probiotic formulation in form of lozenges for delivery of *Enterococcus faecium* CRL 183. Edible films are also used as carrier for probiotics. By such different approaches the probiotics bacteria are delivered in the various regions of gastrointestinal tract. [30, 32, 49, 50, 51, 52]

## RECOMBINANT PROBIOTICS

In the recent era of research and development, recombinant technology have gaining the significant importance in the biotechnological field. The probiotic are not the exception for recombinant technology. Recent advances of this technology are utilized for development of effective and safe probiotics. Recombinant technology involves the transfer of certain gene from one organism to the other organism using specific vector such as plasmid. Due to which the new organism have better and required characters and properties. Probiotics are used for nutrition, food and health from many years. Probiotics have wide range of actions and therapeutic application. The intensity of action, mechanism, safety and specificity of probiotics are differ from species to species and strain to strains. Novel approaches of recombinant technology in probiotics are used to deliver the probiotic molecule at targeted site of mucosal surface as targeted drug delivery in nutrition and health which facilitates accurate targeting of therapeutics. It is essential to carefully evaluate the probiotic strain for virulence and its sensitivity before considering as probiotic. Carrier microorganism used for recombinant probiotic must be therapeutically safe, especially in the cases where they are going to use in diseased conditions. Some probiotic strains are very sensitive to many factors such as heat, gastrointestinal acidity and oxygen and hence it become challenging process. It is essential that the probiotic produced by recombinant biotechnological process should comply with required criteria such as safety, high survival rate during processing, maintenance of viability, heat stability and acid stability. All such aspects should be scientifically validated. In this technology, expressing gene from the strain with good efficacy and potency are separated and such encoded gene are introduced in intended probiotic which having resistance to the most of the stress factors.[53] Recombinant probiotic-Subalin is the new class of probiotic which is developed by the recombinant biotechnological process which produces certain predetermined and intended therapeutic proteins. For the subalin development *Bacillus subtilis* 2335 strain are used. This strain having ability to synthesize of human interferon alpha-2 which shows marked antiviral action. This property of *Bacillus subtilis* 2335 are transformed by plasmid in parent culture. Parent culture shows antibacterial properties. By using these strains, Sorokulova et al. in 1997 developed new probiotic having both antiviral and antibacterial properties. Subalin is free from any kind of adverse effect. When subalin was studied in combination with neoplastic drug cyclophosphamide to assess the effectiveness in antitumor treatment, it was observed that the therapy with subalin showed higher inhibition of growth

of tumor and its spreading as compared to the alone cyclophosphamide. Subalin inhibit growth of tumor due to the ability of recombinant subalin to induce the production of endogenous interferon. *Lactobacillus lactis* strain producing interleukin-10(IL-10) was studied in phase 1 clinical trial on patients with chrohn's disease. Hence the probiotics developed by the recombinant biotechnological process are more superior in every aspects such as potency, spectrum of action, specificity and safety. [35]

## SAFETY OF PROBIOTICS

Probiotics have been used for several years and are regarded as safe. "The origin of many probiotics is from humans which have a long back history of safety along with the use probiotics." This statement is supported for the safety issue of probiotics from the human origin. It has long record of safety. In ambulatory care, almost no side effect has been reported. In 2011, Agency for Healthcare Research and Quality released a report in which, it is stated that, however the existing clinical trials for probiotics reveal no significant evidence of increased risk, and "the current literatures are not equipped to answer the question on the safety of probiotics in interventions studies with confidence."

Due to deficiency of industry standardization and safety issues have troubled the probiotics use with various views against probiotics despite the health benefits. The epidemiological studies in adult shows low rate of systemic infection between 0.05 to 0.40 %. In pregnancy and in infancy they are considered safe. Mainly side effects are reported primarily in those people with underlying medical condition.[13,54] The US Food and Drug Administration (USFDA) designation Generally Recognized as Safe (GRAS) has been applied to probiotics microbes viz; yeast, lactobacilli, bifidobacterium, lactococci etc. Enterobacteria and enterococci not classified under GRAS. When they are added to food, although some systemic safety studies has been carried especially in vulnerable peoples. [55] The standardized and validated safety assessment techniques for novel probiotics and especially genetically modified probiotics needed to be established. Main observed side effects of probiotic strains were fungemia, sepsis, and GI ischemia. These adverse events are observed in patients with critically ill conditions in ICU or patients with immune-compromised complexity.

As per joint FAO/WHO expert committee guidelines, (2002 a.b.) safety of probiotics strain can evaluated by a set of tests viz; antibiotic resistance pattern, eventual side effects, definite metabolic activities, potential virulence factor. There are some factors related to the safety of probiotics for their use as per the safety assessment guidelines as FAO:-

- 1) Description of use of probiotics (dose, format and stability).
- 2) Validation that the product is manufactured under Good Manufacturing Practices specific for the product category.
- 3) Extend of probiotics involved in adverse events.
- 4) Physiological and genetic capacity determination for toxic activities.
- 5) Genetic stability of probiotics.
- 6) Determining the pattern of antibiotic resistance.
- 7) Physiological and genetic capacity determination for pathogenic/ opportunistic pathogenic activities.
- 8) Evaluation of safety of probiotics by the regulatory authority or a panel of expert qualified in the field for



intended use, depending on the product category and requirements.

9) Assessment of metabolic activities.

10) Assessment of adverse effects during study.

For the assessment of safety of probiotics, clinical trials are necessary. But they are very expensive and may cause adverse effects to the human volunteers in clinical trials. Therefore, to avoid such harmful effects, *in vitro* study performed on the probiotics to determine possible mechanism of action.

Criteria for selection of strain in human study are-

- 1) Absence of resistance to clinical/ veterinary antibiotics.
- 2) Non-appearance of virulence factors.

The safety of probiotics documented for infants which is referred to as innocuous substance. There are different safety profiles for the different strains of probiotics. Safety of probiotics classified on the basis of their strain-by-strain basis; dose and interactions with other bacterial strains and pathological conditions. [15, 56, 57, 58, 59]

## CONCLUSION AND CURRENT ASPECTS

Probiotics is one of the important field in research and technology. It is an emerging subject for researchers. Many studies carried out on probiotics in food reduces the risks of diseases to somewhat manner. Now a day's use of probiotics increased significantly because of its successful administration through different routes with minimum side effects. Many of the probiotic species sold commercially in large amount to overcome symptoms of disorders. [9, 35, 61]

Now days, studies are undergoing on the probiotics to discover the emerging applications of probiotics. Current research is going to discover the proper mechanism of action of probiotics in specific disease or disorder. In many causes, prebiotics showed their action but the mechanism remains unclear. Currently, many works going on the formulation aspects of probiotics for its proper administration. Different formulations of probiotics available commercially viz; microcapsules, nanoemulsion, nanosuspension. [10] Many 3D printed tablets also available for better administration of probiotics. Many works going on the 3D printing of probiotics. Probiotics is one of the best tool to cure disease and disorders from new born to adults. [4, 6]

## CONFLICT OF INTEREST

There is no conflict of interest amongst the authors.

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