IJPSR (2019), Volume 10, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 January 2019; received in revised form, 07 April 2019; accepted, 20 April 2019; published 01 September 2019

A QUEST FOR BETTER PROBIOTIC DELIVERY AND FRONTIERS OF PROBIOTIC APPLICATION IN MEDICAL SCIENCE: A CRITICAL REVIEW

Reshmi Chowdhury and Tamalika Chakraborty *

Department of Life Science, Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Road, Panihati, Kolkata - 700114, West Bengal, India.

Keywords:

Probiotic, Micro-encapsulation, Microsphere, Micro-particle, Gastric juice, Bile salt, gut-brain axis, Gut-brain signaling, Alzheimer's, Parkinson's, Psychobiotics, Gastro-entritic disorders, HIV, Cancer

Correspondence to Author:
Mrs. Tamalika Chakraborty

Assistant Professor,
Department of Life Science, Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Road, Panihati, Kolkata - 700114, West Bengal, India.

E-mail: tamalika.chakraborty@gnipst.ac.in

ABSTRACT: Probiotics are live microorganisms that when introduced orally positively contribute to the activity of the intestinal microflora and the health of its host. Various studies showed that probiotics are potentially able to contribute to treatments of many diseases. They may not cure any disease, but can significantly improve the patient's condition and also can prevent many infections. Recent studies confirmed that gut microbiota has a direct connection to the behavior and development of the brain. This review is done in two parts. The first part discusses how micro-encapsulation can improve targeted delivery of probiotics where second part discusses the effects of probiotics on various diseases. On the first half of this review, we will see micro-encapsulation allows core ingredients or probiotics to be separated from the environment by a protective coating which can enhance shelf-life of probiotics. The objective of this review is to study the efficiency of different encapsulation materials and methods to understand and control the delivery of probiotic by the conventional method to improve drug uptake, release and absorption by making it resistant from the harsh environment (Gastric juice and bile salt). On the second half of this review, we will encounter how probiotics are an essential part of the gut-brain axis and gut-brain signaling, how they influence neural development and help in the treatment of various neurodegenerative diseases like Autism, Alzheimer's disease, and Parkinson's disease and how psychobiotics can improve mental health. Probiotics are very helpful in the treatment of various gastroenteritic disorders and also in cases of HIV and Cancer.

INTRODUCTION: "Let food be thy medicine and Medicine be thy food"– Hippocrates. Probiotics are live microorganisms; those can be introduced orally in the gastrointestinal tract or GI tract to improve intestinal microflora and positively contribute to the health of the host.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(9).3993-05

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(9).3993-05

Live bacterial cells are gaining large attention for contributing in treatment of several diseases including kidney failure uremia, cancer, inflammatory bowel disease, cholesteremia, and others. It has been reported that probiotics can suppress the growth of undesirable microorganism in colon and intestine [1].

Benefits of Probiotics: Probiotics are proven to be beneficial and capable of ameliorating health conditions in various diseases which will be discussed in great detail in the second part of this literature below. But to provide a quick view of the beneficial effects of probiotics, it is crucial to

mention few contributions of probiotics. Probiotics regulate immunophysiology by strengthening indigenous micro flora in the gut that acts as a barrier against pathogens. Probiotics eliminate uropathogens and reduce the risk of urogenital infection. Probiotics also lower pH level in the colon, which is helpful in constipation, they help to better absorb protein, minerals, also helpful in lactose intolerance, and IBS (Inflammatory bowel syndrome), colitis, ulcer thus helps to improve the overall digestion process. Probiotics like *Lactobacillus* can alkalinize urine by reducing oxalate as a result decreases chances of nephrolithiasis. Evidence shows that probiotics reduce the duration of symptoms, decrease the severity of the infection and also reduce the frequency of infections that largely contribute to reducing the use of antibiotics thus lower antibiotic resistance. Recent studies show that probiotics are very much efficient in controlling obesity. Probiotics like *L. rhamnosus*, *L. planterum* had an anti-obesity effect on human and animals respectively. Probiotics are capable of preventing eczema in children. Probiotics also found to be helpful in the treatment of Autism, Parkinson's disease, cancer that is discussed later [2].

TABLE 1: SOME PROBIOTIC STRAINS [3, 4, 5]

Name of the microorganisms	About the microorganisms
Bifidobacterium bifidium	It is the most dominant beneficial microorganism in infants and the large intestine. It improves the production of vitamin in the gut, immune response, inhibits harmful bacteria and prevent diarrhea
Bifidobacterium infantis	Helps in reducing IBS symptoms, diarrhea and constipation
Bifidobacterium breve	Colonizes healthy gut community and crowd out bad bacteria
Bacillus subtilis	An endospore-forming probiotic elicits a potent immune response, supports GALT and suppresses the growth of harmful bacteria like *Salmonella* sp
Lactobacillus acidophilus	Improves lactose intolerance, lowers cholesterol levels and improves the production of vitamin K. Important in GALT immune strengthening. Also inhibits *E. coli*
Lactobacillus casei	Boosts immunity, inhibits *H. pylori* and fights infection
Lactobacillus brevis	It can survive the G.I. tract environment, boosts cellular immunity, enhances natural killer cells and kills *H. pylori*
Lactobacillus bulgaricus	A powerful probiotic that fights harmful bacteria those invade our digestive system and is stable enough to withstand acidic gastric juice, it also neutralizes toxins and can produce antibiotics naturally
Lactobacillus rhamnosus	Can survive the G.I. tract. Helps in balancing bacterial flora and keeps skin healthy. Fights urinary tract infection, respiratory tract infection and reduces anxiety by reducing stress hormone and GABA neurotransmitter receptors
Saccharomyces boulardii	It is a strain of yeast that restores the natural microflora in large and small intestine improving intestinal cell growth, used in the treatment of inflammatory bowel disease, reduces inflammation also shows the antimicrobial effect

Properties of Ideal Probiotic:

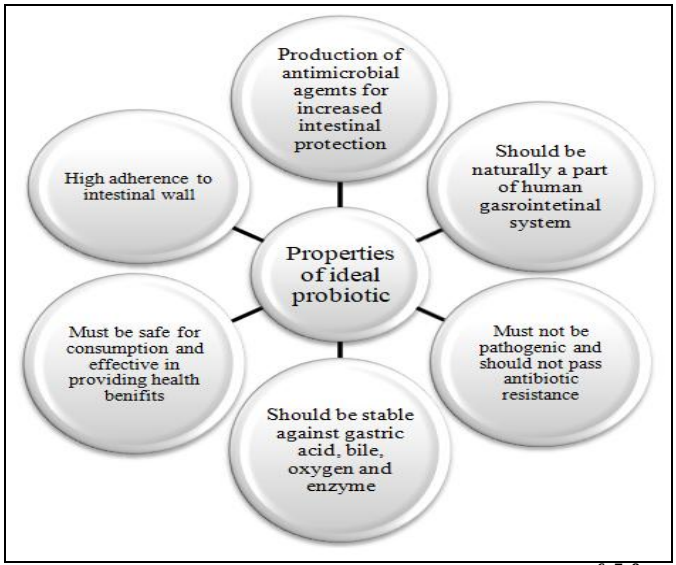

FIG. 1: PROPERTIES OF IDEAL PROBIOTIC [6, 7, 8]

There are various effects of probiotics on biological system like stimulation of the immune system by altering cytokine release, enhanced antibody production and neutral killer cell activity, modulation of dendritic cell, NF-kB and AP-1 pathway, induction of PPAR-g and regulatory T-cells, regulation of apoptosis by improving strict protein phosphorylation, inhibition of proteasomal degradation of proteins, increase in mucus production, sIgA production, enhancement of epithelial cell glycosylation, competition with pathogen for mucosal binding site, production of acids, peroxidase or bacteriocins to prevent bacterial infection, exhibition antimicrobial effect by secretion of antimicrobial peptides like defensin, nitric oxide, inhibition of pathogenic bacterial invasion protecting the epithelial barrier, blockage

of bacterial adhesion to epithelial cells, alleviation of lactose intolerance, cholesterol reduction, tumor targeting [9, 10, 11].

Targeted Delivery of Probiotics: Many mechanisms are available for delivery of probiotics and other drugs to the intestine. Both conventional pharmaceutical process and non-conventional food products are involved. The non-conventional probiotic formulation includes cheese, yogurt, creams, chocolates, milk, meat, *etc*. These are good delivery systems and can be of great benefit for patients. One drawback is, very few products are able to deliver these good bacteria to the intestine. But conventional pharmaceutical formulations differ greatly. The survivability depends on various factors like the formulation process, the viability of dosed bacteria and variation in stability of different species of bacteria in different physiological conditions and ability to adhere to the intestinal wall. Conventional pharmaceutical products tend to be more effective in this regard and much more characterized compared to the food based carrier system. Conventional pharmaceutical formulations include beads, capsules, tablets, *etc*.

Each type of formulation possesses advantages with each having varying amounts of the viable probiotic bacterial cell. The effectiveness of any formulation depends on their ability to deliver the correct amount of viable bacteria at the time of administration, delivery of a correct strain of probiotic bacteria and protection from simultaneously administrated antibiotics. *Lactobacillus* sp. shows greater resistance to gastric acid than other species such as *Bifidobacterium*, where *Enterococci* are more resistant at gastric pH (2.0-3.0) than other bacteria tested for 60 min.

Bile tolerance is another important factor, because probiotic bacteria interact with bile on entry into the small intestine. This issue is not seen in case of naturally occurring probiotic bacteria. Because of being commonly exposed to bile salt in the intestine, they develop bile tolerance. Food delays the absorption of various medicines and probiotics and leads to the improper availability of given dosage. So, conventional methods like microsphere or microparticle can be taken under consideration to study the increase or decrease in the rate of the viability of probiotics. To be therapeutically active sufficient number of live probiotic must arrive at the intestine which is 106-107 cfu [12, 13, 14]. Here, we are going to discuss the microencapsulation of probiotic using microsphere and microparticle.

Micro-encapsulation: It allows core ingredient or probiotic to be separated from the environment by a protective coating. Encapsulation is the most widely applied technique in research and industrial practices to improve the survival of probiotics, owing to its universal efficacy and little influence on the embedded microorganisms. Within the context of the present work, the encapsulation material is expected to be a food grade agent. The basic principle is that the probiotic bacteria are immobilized in such material and thus protected from the harsh conditions [15].

Parameter for Encapsulation of Probiotics:

- Easy techniques and accuracy of particle size;
- Encapsulation materials should have mechanical strength as required;
- Ability to release the cells at the target site is important;
- The material used should be able to withstand the adverse environment in vivo and should protect the cells;
- Biocompatible & biodegradable encapsulation materials are highly favored;
- It should be non-toxic [16-19].

Microspheres: Microspheres are spherical shells those are usually made up of biodegradable or resorbable plastic polymers, those are of very small diameter, usually in the micrometer or nanometer range, and are often filled with substances (as a drug or antibody) for release as the shells are degraded. Hypromellose is considered suitable in the preparation of mucoadhesive microspheres due to its favorable mucoadhesive properties, and it is safe for oral consumption by a human.

Another suitable encapsulating agent is whey protein, a byproduct of the cheese industry that causes high environmental contamination. Different strategies for producing microcapsule with whey protein include spray drying, cold-induced gelation, complex coacervation and a

combination of different methods. EC (ethyl cellulose) is derivative of cellulose in which some of the hydroxyl groups of anhydrous glucose units are modified into ethyl ether groups, largely called as non-ionic ethyl ether of cellulose. EC is used for microencapsulation of various pharmaceuticals to stabilize them against interaction, hydrolysis oxidation. It is also used as a matrix forming or coating agent to achieve the controlled release of antibiotics and probiotics. An EC microparticle can be considered as a mini-osmotic pump.

It is possible to fine-tune the release kinetics of EC microparticles by altering osmolality of the dissolution medium or formulations and EC film's mechanical characteristics can be altered by selecting proper EC molecular weight, EC substitution grades, and coating weight and size of pores. The release of a highly or sparingly soluble drug is considerably reduced when osmolality of dissolution medium is increased, causing a reduction in osmotic pressure across the release controlling membrane. Drug release reduces considerably with the increase in EC molecular weight. Higher molecular weight results in increase in the polymer chain and thus results in the stronger film, increased elasticity, and tensile strength. Stronger films may resist greater hydrostatic pressure and damage of the film due to channel formation or a stress fracture. Lower molecular weight, faster release where higher will be the molecular weight slower will be the release.

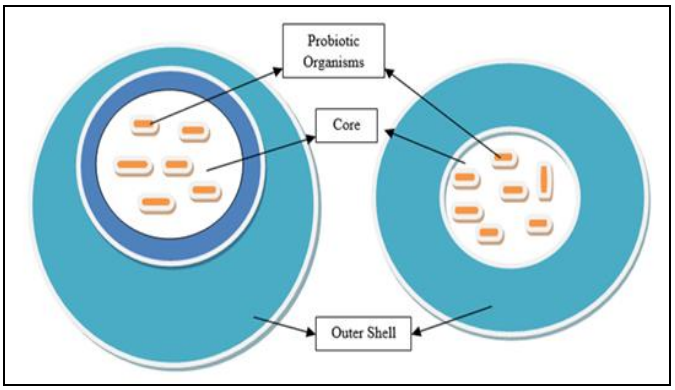

FIG. 2: STRUCTURE OF PROBIOTIC COATED MICROSPHERE

TABLE 2: TECHNOLOGIES TO PROCESS MICROSPHERE [1, 2, 3]

Technology	Principle feature	Advantage	Disadvantage
Spray drying, freeze-drying & fluidized bed drying techniques	Drying of the aqueous medium of probiotic and carrier material and getting into concentrated powder form	Less complicated	Release of entrapped probiotics in the dosage form and less viability
Extrusion	Gel bead formation by extrusion of hydrocolloidal probiotic mixture in a gel-forming solvent	Simple, able to retain a high number of cells, automated and uniform size beads	Size and shape of beads depending on the diameter of the nozzle and distance between nozzle and gelling solution. Beads have a greater size than capsules
Emulsification	Dispersing probiotic containing disperse phase in the continuous phase	Produces very similar size capsules compared to beads	Complicated, expensive process, use of oil, un-uniformed capsule size

TABLE 3: EXCIPIENTS USED FOR MICROENCAPSULATION [17, 18, 19]

Polymer	Characteristics	Remark
Alginate	Insoluble in acidic media. 60-80 degree C. temperature is needed to dissolve it.	Protects the cells against acidic condition
Carrageenan	Kappa carrageenan and iota carrageenan has gelation property due to their structural conformation. Dissolves at 60-80 degree C. Solidifies after cooling	Forms a gel and entraps cell
Chitosan	Positively charged polysaccharide. Insoluble at higher pH than 5.4, forms a negatively charged semi-permeable membrane	Can be used in combination with other polymers like alginate, for providing stability
Cellulose acetate phthalate	pH-dependent cellulose derivative, insoluble at pH below 5 but soluble in pH greater than 6	CAP cannot form gel beads by gelation; the capsule is developed by emulsification. It's a great coating agent
Locust bean & starch	Specific interaction occurs during mixing with other polymers	Used by mixing with alginate or carrageenan to develop gel beads

In non-conventional food product, cheddar cheese is good for delivering a variety of probiotic bacteria like *Lactobacillus* and *Bifidobacterium*. Increase in intestinal flora has been observed after ingestion of probiotic cheese. Milk has also been considered as a good delivery medium for probiotics. Delivery of *Lactobacillus* sp. showed an increase in colony numbers after administration through milk. The Casein micro peptide is a glycopeptide containing nitrogen and amino sugars; those works as growth factors for *Bifidobacterium*.

Lactobacillus rhamnosus cell count increases when administrated through yogurt. The ability of yogurt to deliver probiotic was found to be low when compared to other products due to its acidity and oxygen content. It is especially not favorable for anaerobic *Bifidobacterium*. Due to higher fat content chocolate and ice-cream provide greater protection to probiotic against gastric juice and bile salt compared to yogurt [20-22].

Microparticle Formulation: Microparticles are small solid particles within the size range 1-200 µm. Depending on the type of drug is being encapsulated the method of microparticle formation is determined, and the drug is dissolved, entrapped and encapsulated in the microparticle matrix. Biodegradable polymers have been of long interest in controlled release technology for their ability to be reabsorbed by the body. These microparticles show bulk erosion hydrolysis. The release rate of both hydrophilic and hydrophobic drugs have changed significantly when incorporated through micro-particles. Pappas *et al.,* 1995 drugs were incorporated into non-degradable silicone or degradable gelatin. The drug released from the microparticle within the silicone didn't exhibit high release *in-vitro*.

Microparticle size range from 1-100µm. Microparticle designed for parental drug delivery can be composed of a variety of different materials with different physical characteristics such as biodegradability, biocompatibility, injectability, sterility, compatibility and stability. To prepare micro particles several techniques are applied. Most commonly used are organic solvent evaporation and/or extraction method. Depending upon the solubility of drug simple or multiple emulsion technique, oil-in-water (o/w) and water-in-oil-in-water (w/o/w) methods are used. In o/w technique, lipophilic drug is dissolved into an organic phase, which is dispersed into the outer aqueous phase. Then, upon contact organic solvent diffuses into the external water phase and evaporates at its surface. The drug is precipitated and entrapped by the polymer.

If the drug is hydrophilic, then w/o/w technique is used where the direct contact of the drug-containing phase with an outer water phase is avoided. An aqueous solution of the drug is emulsified into an organic phase containing dissolved polymer. Water and organic solvent emulsion are dispersed into an outer aqueous phase. During solvent diffusion/ evaporation, the polymer precipitates and the drug get incorporated. Albumin microparticles are hugely used because they are biodegradable, non-antigenic, and non-toxic, also can control physiochemical characteristics of the micro-particle produced and are readily available [22-25].

A spectrum of Probiotic Application: Recent Studies and Promises:

Gut-Brain Connection To understand how gut microorganisms are involved in gut-brain crosstalk, it is necessary to understand how the immune system is directly connected to our cognitive health as we all know gut microflora is an inseparable part of our immune system.

Psychoneurology pays very deep attention to stress and how it modulates the body's defense against disease and thus sheds light on how resilience buffers stress elicited changes. Resilience is developing a positive mindset and adapting to adverse situations, trauma, loss, relationship related and financial stress to recover. The relationship between stress and immunity is bidirectional because immune mediators influence how the brain processes information and responds to it. It can potentially be modulated with the help of probiotics [26].

Exposure to acute stress increases levels of cortisol & glucocorticoid hormone. Those usually reduce inflammation by reducing the release of pro-inflammatory cytokines. Individuals exposed to acute stress first adapted to increased cortisol level by reducing the responsiveness of immune cells to

cortisol which leads to failure in regulation of immune response [27, 28]. Even sickness can lead to symptoms of depression. Sometimes due to polymorphism in cytokine gene inflammatory and anti-inflammatory cytokines get increased or decreased. Infection, leaky gut or stress results into systemic inflammation and activation of IDO1 (Indoleamine 2, 3 dioxygenases) which induces the release of inflammatory mediators resulting into somatic symptoms like reduced appetite, fatigue, sleep disorder, *etc.* It also leads to increased production of Kynurenine that passes through the blood-brain barrier and converts into neurotoxic metabolites of Kunureine. Which in turn produces cognitive/ affective symptoms of depression. After that brain macrophages & microglia get activated and CD8+ T cells recruited in the meninges and choroid plexus, and macrophages get deactivated, and recovery starts [29]. The gut is considered a second brain because of the huge number of neurons in gut walls, but the connection between gut microorganisms and brain are being studied only recently [30, 31, 32]. It is also considered as a new paradigm in neuroscience [33].

Recently from the germ-free studies, scientists have found that gut microorganisms play a pivotal role in brain function, the establishment of the blood-brain barrier, myelination, and functioning of neurotransmitter systems such as serotonin [34]. There are various parallel routes through which gut microorganisms and the brain can communicate with each other. One big example is the Vagus nerve channel [30, 31, 32]. *Lactobacillus* strain produces GABA that binds to GABA receptors and shows significant impact on behavior, but those who were vagotomised had no behavioral change [35]. Gut microorganisms like *Bifidobacterium* produce tryptophan, which we also acquire from foods, get metabolized by IDO1 and results in an increase in Kynurenine level. Some microbial strains like *Lactobacillus reuteri* can modulate Kynurenine by downregulating IDO1.[36]

Gut and Hypothalamic Pituitary Adrenal (HPA) Axis: The HPA axis is the central stress response system. Under stress corticotrophin-releasing hormone (CRH) gets released from the hypothalamus and induces ACTH (Adrenocorticotrophic hormone) release from the adrenal cortex and pituitary gland. It can lead to activation of sympathetic and parasympathetic nerves for extended periods which in turn slows down the digestive process and also alters gut barrier [37].

Memory and Gut Micro Flora Link: One major property that controls cognitive function is neuroplasticity. It is a lifelong change which involves the alteration of neural synapses, neurons, pathways, vesicular cell, and glial cells. It involves deletion of the neural connections, those are no longer necessary, to strengthen the useful memories and neural connections. Brain-derived neurotrophic factor (BDNF) contributes largely to Neuroplasticity. A type of ionotropic glutamate receptor called N-methyl-D-aspartate (NMDA) receptors found in nerve cells when binds to glutamate and glycine allow cations to flow through cell membrane potential of 0 mV [38, 39].

Dysfunction of the NMDA receptor has found to be very common in various nervous system disorders, including ischemic brain injury and neurodegenerative diseases, depression, schizophrenia. Hyperactivity or hypoactivity can contribute to physiopathology of the diseases [40]. *Bifidobacterium infantis, Lactobacillus farciminis,* and *Lactobacillus helveticus* were found helpful in reducing stress and improving cognitive health [41, 42, 43]. The significantly lower amount of *Bifidobacterium* sp. was found in individuals with major neurogenic disorders than healthy people [44]. Administration of probiotics like *Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum* help in improving insulin metabolism and decrease oxidative stress [45]. Significantly high improvement was seen in the condition of a patient diagnosed with Alzheimer's disease after administration of probiotics like *L. acidophilus, L. casei, B. bifidum, L. fermentum* [46]. Probiotics containing *L. rhamnosus* and *Bifidobacterium animals* were found to be especially helpful for patients diagnosed with schizophrenia. Some studies suggest that ingestion of *Bifidobacterium longum* 1714 helps in improving memory [47].

Gut Microbiota & its Link to Autism-Like Disorders: Various studies have been done to establish the effect of gut microorganisms in diseases like Autism. Autism-like behavior was

induced in Pups when pregnant BALB/c females were to valproic acid. Afterbirth of offsprings they were exposed to the social environment for social behavior test in which they showed less social behavior. After examination of inflammatory markers in the brain and intestinal tissue, an increase in expression of markers was observed. Serotonin level in the cortex, amygdala and small intestine of male pups decreased [48].

In another experiment behavior, of germ-free (GF) mice who were colonized by bacteria after weaning was compared to mice those were conventionally colonized. As a result GF mice were showing less social involvement and novelty compared to conventional mice. But these behaviors normalized after bacterial colonization [49].

Effect of Gut Microbiota on Amygdala and Hippocampus: P. Luczynski *et al.,* demonstrated how the gut microbiota could influence brain morphology. Amygdala and hippocampus are two vital regions of the brain those regulate both behavioral and physiological characteristics.

They performed a germ-free experiment with GF (germ free) and CC (collaborative cross) mouse model. GF & CC mice were divided into two groups, one for stereological study and another for the study of dendritic morphology. Results found after the study was quite unavoidable. GF those lacked gut microbiota had enlarged amygdala & hippocampus where total brain volume was the same. So, definitely enlargement of amygdala & hippocampus did not happen due to whole brain expansion. With this dendritic hypertrophy in BLA inhibitory aspiny interneurons and excitatory pyramidal neurons were seen in GF mice. 81% more axospinous synapses were detected in BLA pyramidal neurons of GF mice. The germ-free status also induced atrophy in both hippocampal pyramidal neurons and dented granule cells. These findings showed that gut microbiota is essential for proper amygdalar and hippocampal morphology [50].

Probiotics as a Treatment of Alzheimer's Disease: Recent studies suggest that deposition of amyloid beta (Aβ) lies at the heart of Alzheimer's disease. *Lactobacillus* is one of the widely used probiotics. *Lactobacillus reuteri* ELF has been reported to be able to decrease amyloid beta (Aβ) and postsynaptic density protein (PSD). In fact, it can reduce Tau protein. It is also reported that *Lactobacillus reuteri* can suppress the expression of the glial fibrillary acidic protein (GFAP). It can also increase COX activity in brain mitochondria significantly. By this way, it promises an effective treatment to prevent degenerative brain disease including Alzheimer's disease [51, 52, 53, 54].

Gut Microbiota in Prevention of Parkinson's Disease (PD): Another widespread neuro-degenerative disease is Parkinson's disease. It is the second most common neurodegenerative disease in the United States with an average of 1 in every 500 people. 6 million people are carrying this disease worldwide. Aggregation of protein α-synuclein (αSyn) results in motor dysfunction, which is the hallmark pathology of this disease. During the experiment under GF (germ-free) condition or when microbiota depleted with antibiotic treatment, transgenic mice expressing excess human αSyn led to a reduction in microglial activation, αSyn inclusion, and motor deficit. But these things do not happen in healthy controls. Healthy mice were inoculated with microorganisms derived from the body of a Parkinson's patient; it resulted in motor dysfunction [55]. It suggests that gut microorganisms regulate signaling pathways.

Rise of Psychobiotics: Psycobiotics are good bacteria when ingested in adequate amount impart good mental health and helps in brain and neuronal development. The Nobel laureate Metchnikoff, for the first time, introduced the concept of psychobiotics when he noted a fact that individuals of Bulgaria who used to consume fermented milk in large quantity had a longer life span than the rest.

Some recent studies included probiotic fibers in Psychobiotic because it works as a growth-promoting factor for gut microbiota [56]. *Bifidobacterium longum* 1714 strain was reported to improve cognitive function & behavior. Improvement in hippocampal visuospatial memory was noted. Frontal midline electroencephalographic mobility was also enhanced [57].

In a study, pregnant women were treated with *Lactobacillus rhamnosus* HN001 which resulted in lower anxiety and depression in the postpartum

period than those who did not receive the above Psychobiotic [58].

Thereby, above findings open up the door for a new field of study and promises new genera of personalized medicines, where based on individual's need each person will get their personalized combination of probiotics.

Influence of Probiotics on Gastrointestinal Health: Use of probiotics for the betterment of intestinal health is not new. The contribution of gut microorganisms in maintaining intestinal health has been supported by a large number of published literature. Widely studied probiotic microorganisms include *Lactobacillus* sp., *Bifidobacterium* sp., *Escherichia coli*, *Bacillus* sp., and *Streptococcus* sp. Probiotics shield us from various intestinal disorders in many ways. All the mechanisms lead to 'Colonization Resistance'. Probiotics prevent pathogens from colonizing in our intestine.

TABLE 4: MECHANISMS OF DISEASE PREVENTION BY GASTROINTESTINAL MICROFLORA [59, 61]

Actions	Mechanisms
Competition for nutrients	Probiotics compete with pathogenic microorganisms for food and exclude them by preventing them from nutrient uptake
Production of inhibitory substances	Probiotics produce various substances like hydrogen peroxide, organic acids, bacteriocins that eliminates live pathogens and also eliminate toxins
Degradation of receptors	Probiotics like *Saccharomyces boulardii* help in degrading toxin receptors on intestinal mucosa
Blocking of adhesion	Probiotics not only compete for the nutrients but also compete for adhesion site. So, probiotics adhere to epithelial mucosa. In this process, they exclude pathogens from the gut
Immunity boosting	Increase in good bacteria also boosts immunity by inducing both specific and nonspecific immunity. Example: *Lactobacillus* sp. is capable of inducing an immune response during rotavirus infection

Crohn's disease and ulcerative colitis are two inflammatory bowel diseases. Crohn's disease is caused by inflammation of the digestive tract. Inflammation can take place in different areas of the digestive tract, spanning from mouth to anus. Crohn's disease can be genetic, if it acquired hereditarily or it can be due to an autoimmune disorder, where mistakenly immune cells detect digestive tract microflora as foreign. Non-steroid anti-inflammatory drugs like Ibuprofen and birth control pills can increase the chances of getting Crohn's disease [60].

Ulcerative colitis is long lasting inflammation of the colon. It can be caused by bacteria like *C. defficile* or autoimmune disorder, malnutrition. *E. coli* Nissel strain (Serotype O6:K5: H1) was found to be helpful in the treatment of colitis. *Bifidobacterium* sp. was found to be especially helpful in Crohn's disease [62].

Irritable bowel syndrome (IBS) is caused by hypersensitivity of the colon, which causes spasm, leading to chronic pain, diarrhea or constipation. In physiological studies, it was found that alteration in intestinal microbiota has a profound effect on IBS [63]. A study in Poland suggests that *L. planterum* can significantly reduce abdominal pain in IBS patients [64].

Helicobacter pylori are the etiological agent of chronic gastroenteritis and gastric ulcer which can lead to stomach cancer. Studies showed that *Lactobacillus* plays an antagonistic role against *H. pylori* [65].

Not only was that *L. acidophilus* found helpful in hepatic encephalopathy because of their ability to reduce urease which is first and foremost reason behind hepatic encephalopathy. Ammonia gets produced in the intestine by bacterial urease, and increased level of ammonia in the blood leads to this disease [66].

Effect of Gut Microbiota in HIV: HIV is one of the major challenges for medical science. Worldwide 36.9 million people are HIV positive. Among them, 1.8 million are children (age <15) [67]. Till today there is no complete cure for HIV. One hallmark pathology of HIV is decreasing in CD4+ count. It is because they bind to CD4+ T-lymphocytes, invade them and grow inside them. At the end of the life, cycle T-lymphocytes get ruptured, and new progeny of HIV get released.

This process is repeated until all the CD4+ T cells are destroyed. Almost all HIV infected patients encounter impaired gastrointestinal (G.I.) tract, which in turn causes microbial translocation, immune activation, and progression of the disease. Other symptoms like diarrhea and low immunity are also seen.

One good news is recent studies on the effect of probiotics in HIV infected individuals were very promising. A study with 44 HIV patients showed that when they were supplemented with *Saccharomyces boulardii* for over 4 weeks, there was a significant decrease in LPS binding protein and IL-6 those were responsible for translocation and inflammation respectively, compared to those supplemented with placebo [68].

In another study, *Lactobacillus rhamnosus* effectively elevated G.I. tract, improved nutrient uptake and increased tolerance to ARV (Anti-retroviral) treatment [69]. Another study performed with 25 HIV positive women; among them, 18 women were experiencing serious diarrhea, flatulence, and nausea. They were supplemented with probiotics and their condition improved within 30 days of probiotic uptake. But those symptoms reappeared after 3 months of discontinuation. So, it suggests continuous use of probiotics [70]. A meta-analysis has shown that probiotics can decrease diarrhea and fever in HIV positive children [71].

During a study 8 out of 12 HIV patients consumed probiotic yogurt for 15 days and there was a four-fold increase in CD4+ count [70]. Another group of HIV positive patients receiving ARV (Anti-retroviral) treatment up took probiotic in the daily diet and count of CD4+ cells increased by 62 CD4+ per year [72]. Another study showed HIV positive women with less than 200 CD4+ cells had a profound increase in CD4+ cell with a mean of 93 cells/µl where those who received placebo had a decrease in CD4+ cells by mean of 69cells/µl [73].

Effects Probiotics in Cancer: Cancer is considered as a second most fatal disease in the entire world with 14.1 million cases which are expected to increase up to 20 to 21 million with up to 13.2 million casualties worldwide by 2030. Cancer is the uncontrolled proliferation of cells with less sensitivity to growth factors, thus resulting in low quality of the cells. A hallmark of cancer is metastasis. Metastasis is the ability of cancer cells to detach from the primary site and develop secondary tumors on a distant tissue organ [74]. After thorough research on different cancer cell lines probiotics were found to have antiproliferative effects on various cancer cells like myeloid leukemia cells, stomach, breast, cervix, colon cancer cells. It was reported that *Lactobacillus kefiri* showed an apoptotic effect on myeloid leukemia cells. Probiotics like *L. rhamnosus* strain GG & *B. adolescentis* SPM0212 had large antiproliferative and inhibitory effects on gastric cancer cells, three colon cancer cell lines SW 480, $CaCO_2$ and HT-29. [75-85]

Lactobacillus casei Shirota (LcS) was found effective for breast cancer, cervical cancer, and HPV positive intraepithelial lesion [86, 87]. *Enterococcus lactis* IW5 obtained from human gut found to be able to decrease viable cancer cells of different cell lines like HeLa, MCF-7, HT-29, $CaCO_2$ and AGS [88]. Mechanisms responsible for the anticancerous effects of probiotics are poorly known, but some reports suggest that mechanisms like enhancements of gut barrier function and immune system function, degradation of carcinogens and modulation of gut microbiota are behind these actions. From the above information, it is quite evident that probiotics are crucial in maintaining our health. It not only opens a new frontier, but also promises a better future. Thus, demands more attention and research.

DISCUSSION: From the first part of the review it is evident that microencapsulation by the formation of microsphere and microparticle can significantly control the release of drug or probiotic. By microencapsulation, drug release can be reduced by approximately 20-25%. It is also able to protect drug or probiotic from the harsh effect of gastric fluid and bile salt. With the increase in molecular weight of encapsulating polymer, the rate of drug release decreases. One major noticeable matter is microsphere used for both drug and probiotics, but microparticles are mainly used for drugs. One possible reason is the presence of less amount of water in microparticles than microsphere, and this low water activity can be fatal for the microbial cell.

That's why lyophilization is detrimental to the survival of bacteria, so protection from the harsh effects of freeze-drying is most often needed. From the second part of the review, we also get a brief idea about how pivotal role gut microbiota plays in maintaining our health.

Probiotics not only contribute to gastrointestinal health, but also helps to fight various neurodegenerative diseases like Alzheimer's disease, Parkinson's disease and also modulates our behavior. Probiotics are also proven to be beneficial in the treatment of diseases like HIV and boost immunity.

CONCLUSION: From the above study, we can easily conclude that probiotics are and will be very effective in the treatment of many complicated diseases. That is why it has now become more important to improve administration processes of probiotics so that we can effectively introduce a less amount of probiotics and get better results. For that encapsulation is considered an excellent idea which is novel and demands more study.

Encapsulation of probiotic microorganisms or drugs increases their shelf life. It protects them from gastric juice; thus the uptake of less amount of medicine becomes more effective for the most amount of administered drug reaches to destination and gets absorbed. It is also effective in targeted drug delivery.

Microspheres appeared to encapsulate more drugs than micro-particles due to greater surface area. From the above study it is evident that increase in the concentration of the polymer increases entrapment efficiency due to increase in surface area but tends to decrease the release due to complex polymeric mesh-work and that is why micro-particles are recommended for drug encapsulation, small particles of drugs can diffuse more quickly through those mesh works than microorganisms. Micro-particles are used more than microspheres for drugs, not microorganisms also because of their less water content and less surface area. To entrap microorganisms microspheres are preferred than micro-particles. Microorganisms survive well in microspheres because they get the required moisture content to survive.

FUTURE ASPECT:

- Enhancement of the efficacy of probiotic, targeted drug delivery.
- Immune modulation.
- Treatment of diseases like intestinal colitis, IBS, neurodegenerative diseases, HIV and cancer.
- Exploration of new beneficial organisms.
- Use of microencapsulation as a gene carrier.
- Improvement of food supplement.

ACKNOWLEDGEMENT: Guide is just like that pole star in the sky that meticulously shows the right direction to reach the ultimate goal, in the boundless field of research work. The guide is not only a wise & trusted advisor, but also a dedicated & earnestly endeavoring person for authenticity in the field. It is very difficult for me to express the deep debt of gratitude in words. 'Thanks' will of no meaning in front of their amazing image. Saying thanks is not a big task, since there is no other way which can better express my feeling of love & gratitude with regards to my mentor Mrs. Tamalika Chakraborty, (Asst. Prof.), for her active guidance, high technical caliber, continuous supervision & constant encouragement throughout the course of this research work. It was an enriching experience to work under their esteemed presence. I am thankful to all of my teachers of Guru Nanak Institute of Pharmaceutical Science and Technology, Panihati, Kolkata, 700114 for their kind help. Above all, I submit my silent and humble prostration at the lotus feet of my parents whose blessing has enabled me to complete our dissertation work on time.

CONFLICT OF INTEREST: None

REFERENCES:

1. Rokka S and Rantamaki P: Protecting probiotic bacteria by microencapsulation: challenges for industrial applications. European Food Research and Technology 2010; 231(1): 1-12.
2. Kechagia M, Basoulis D and Konstantopoulou S: Health benefits of probiotics: A review. ISRN Nutrition 2013; 1-7.
3. Santiago GL, Verstraelen H, Poelvoorde N, De Corte S, Claeys G and Trog M: A pilot study evaluating the safety of vaginal administration of a multi-particulate pellet formulation. Eur J Pharm Biopharm 2009; 73(3): 399-03.

4. Douglas LC and Sanders ME: Probiotics and prebiotics in dietetics practice. J Am Diet Assoc 2008; 108(3): 510-21.
5. Mombelli B and Gismondo MR: The use of probiotics in medical practice. Int J Antimicrob Ag 2000; 16(4): 531-6.
6. Holzapfel WH, Haberer P, Snel J, Schillinger U and Huisin't Veld JHJ: Overview of gut flora and probiotics. Int J Food Microbiol 1998; 41(2): 85-101.
7. Janer C, Pelaez C and Requena T.: Caseinomacropeptide and whey protein concentrate enhance *Bifidobacterium lactis* growth in milk. Food Chem 2004; 86(2): 263-7.
8. Hove H, Norgaard H and Mortensen PB: Lactic acid bacteria and the human gastrointestinal tract. Eur J Clin Nutr 1999; 53(5): 339-50.
9. Natural Remedies (https://draxe.com/natural-remedy/) Nutrients & Supplements (https://draxe.com/natural-remedies-category/nutrients-supplements/) Probiotics Benefits, Foods and Supplements.
10. Gibson GR and Roberfroid MB: Dietary modulation of the human colonic microbiota. Introducing the concept of prebiotics. J Nutr 1995; 125: 1401-12.
11. Crittenden R, Bird AR, Gopal P, Henriksson A, Lee YK and Playne MJ: Probiotic research in Australia, New Zealand and the Asia-Pacific region. Curr Pharm Des 2005; 11(1): 37-53
12. Govender M, Choonara YE, Kumar P, du Toit LC, van Vuuren S and Pillay V: A review of the advancements in probiotic delivery: Conventional *vs.* non-conventional formulations for intestinal flora supplementation. AAPS PharmSciTech 2013; 15(1): 29-43.
13. Minelli EB, Benini A, Marzotto M, Sbarbati A, Ruzzenente O and Ferrario R: Assessment of novel probiotic *Lactobacillus casei* strains for the production of functional dairy foods. Int Diary J 2004; 14(8): 723-36.
14. Phillips M, Kailasapathy K and Tran L: Viability of commercial probiotic cultures (*Lactobacillus acidophilus*, *Bifidobacterium* sp., *L. casei*, *L. paracasei* and *L. rhamnosus*) in cheddar cheese. Int J Food Microbiol 2006; 108(2): 276-80.
15. Gilliland SE and Walker DK: Factors to consider when selecting a culture of *Lactobacillus acidophilus* as a dietary adjunct to produce a hypocholesterolemic effect in humans. J Dairy Sci 1990; 73(4): 905-11.
16. Brazel CS: Microencapsulation: offering solutions for the food industry. Cereal Foods World 1999; 44(6): 388-93.
17. Kim B-S, Baez CE and Atala A: Biomaterials for tissue engineering. World J Urol 2000; 18(1): 2-9.
18. Tønnesen HH and Karlsen J: Alginate in drug delivery systems. Drug Dev Ind Pharm 2002; 28(6): 621-30.
19. Kuang SS, Oliveira JC and Crean AM: Micro-encapsulation as a tool for incorporating bioactive ingredients into food. Critical Reviews in Food Science and Nutrition Taylor & Francis 2010; 50(10): 951-68.
20. Possemiers S, Marzorati M, Verstraete W and Van de Wiele T: Bacteria and chocolate: a successful combination for probiotic delivery. Int J Food Microbiol 2010; 141(1-2): 97-103.
21. Ong L, Henriksson A and Shah NP: Development of probiotic Cheddar cheese containing *Lactobacillus acidophilus*, *L. casei*, *L. paracasei* and *Bifidobacterium spp.* and the influence of these bacteria on proteolytic patterns and production of organic acid. Int Diary J 2006; 16(5): 446-56.
22. Mombelli B and Gismondo MR: The use of probiotics in medical practice. Int J Antimicrob Ag 2000; 16(4): 531-6.
23. Peppas BL: Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery. Int J Pharm 1995; 116(1): 1-9.
24. Mathew ST, Devi SG and Sandhya KV: Formulation and evaluation of ketorolac tromethamine-loaded albumin microspheres for potential intramuscular administration. AAPS Pharm Sci Tech 2007; 8(1): 71-79.
25. Mansour HM, Sohn M, Al-Ghananeem A and Deluca PP: Materials for pharmaceutical dosage forms: molecular pharmaceutics and controlled release drug delivery aspects. Int J Mol Sci 2010; 11(9): 3298-22.
26. Dantzer R and Kelley KW: Stress and immunity: an integrated view of relationships between the brain and the immune system. Life Sci 1989; 44: 1995-08.
27. Cohen S: Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. PNAS 2012; 109: 5995-99.
28. Cohen S: Types of stressors that increase susceptibility to the common cold in healthy adults. Health Psychol 1998; 17: 214-23.
29. Dantzer R, O'Connor JC, Freund GG, Johnson RW and Kelley KW: From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci 2008; 9: 46-56.
30. Dinan TG and Cryan JF: The microbiome-gut-brain axis in health and disease. Gastroenterol Clin North Am 2017; 46: 77-89.
31. Dinan TG and Cryan JF: Gut instincts: microbiota as a key regulator of brain development, ageing and neuro-degeneration. J Physiol 2017; 595: 489-03.
32. Dinan TG, Stanton C and Cryan JF: Psychobiotics: a novel class of psychotropic. Biol Psychiatry 2013; 74: 720-26.
33. Mayer EA, Knight R, Mazmanian SK, Cryan JF and Tillisch K: Gut microbes and the brain: a paradigm shift in neuroscience. J Neurosci 2014; 34: 15490-96.
34. Luczynski P: Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior. Int J Neuropsychopharmacol 2016; 19: 8
35. Bravo JA: Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse *via* the vagus nerve. Proc Natl Acad Sci 2011; 108: 16050-55.
36. Marin IA: Microbiota alteration is associated with the development of stress-induced despair behavior. Sci Rep 2017; 7: 43859.
37. Gruenwald J, Graubaum HJ and Harde A: Adv Therapy. Springer Healthcare Communications 2002; 19: 141.
38. Dingledine R, Borges K, Bowie D and Traynelis SF: The glutamate receptor ion channels. Pharmacol Rev 1999; 51(1): 7-61.
39. Liu Y and Zhang J: Recent development in NMDA receptors. Chinese Medical Journal 2000: 113(10): 948-56.
40. Zhou Q and Sheng M: NMDA receptors in nervous system diseases. Neuropharmacology Elsevier Ltd., 2013; 74: 69e75.
41. Allen AP, Dinan TG, Clarke G and Cryan JF: A psychology of the human brain-gut–microbiome axis. Soc Personal Psychol Compass 2017; 11: e12309.
42. Ait-Belgnaoui A, Durand H, Cartier C, Chaumaz G, Eutamene H, Ferrier L, Houdeau E, Foramonti J, Bueno L and Theodorou V: Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to acute psychological stress in rats. Psychoneuro-endocrinology 2012; 37: 1885-95.
43. Liang S, Wang T, Hu X, Luo J, Li W, Wu X, Duan Y and Jin F: Administration of Lactobacillus helveticus NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience 2015; 310: 561-77.

44. Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, Ota M, Koga N, Hattori K and Kunugi H: Possible association of *Bifidobacterium* and *Lactobacillus* in the gut microbiota of patients with major depressive disorder. J Affect Disord 2016; 202: 254-57.
45. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, Memarzadeh MR, Asemi Z and Esmaillzadeh A: Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition 2016; 32: 315-20.
46. Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA and Salami M: Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: A randomized, double-blind and controlled trial. Front Aging Neurosci 2016; 8: 256.
47. Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CLG, Schweinfurth LAB, Goga J, Khushalani S and Yolken RH: Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: A randomized, placebo-controlled trial. Prim Care Companion CNS Disord 2014; 16(1): 13m01579.
48. De Theije CG: Intestinal inflammation in a murine model of autism spectrum disorders. Brain Behavior Immunity 2014; 37: 240-247.
49. Desbonnet L, Clarke G, Shanahan F, Dinan TG and Cryan JF: Microbiota is essential for social development in the mouse. Mol Psychiatry 2014; 19(2): 146-148.
50. Luczynski P, Whelan SO, O'Sullivan C, Clarke G, Shanahan F, Dinan TG and Cryan JF: Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. European Journal of Neuroscience 2016; 44, 2654-66.
51. Naseer MI, Bibi F, Alqahtani MH, Chaudhary AG, Azhar EI, Kamal MA and Yasir M: Role of gut microbiota in obesity, type 2 diabetes and Alzheimer's disease. CNS & Neurological Disorders - Drug Targets 2014; 13: 305.
52. Köhler CA, Maes M, Slyepchenko A, Berk M, Solmi M, Lanctôt KL and Carvalho AF: The gut-brain axis, including the microbiome, leaky gut and bacterial translocation: Mechanisms and pathophysiological role in Alzheimer's disease. Current Pharmaceutical Design 2016; 22: 6152.
53. Junges VM, Closs VE, Nogueira GM and Gottlieb MGV: Crosstalk between gut microbiota and central nervous system: A focus on Alzheimer's disease. Current Alzheimer Research 2018; 15: 1179.
54. Jo SY, Daejeon KR, Min SH, Daejeon KR, Yun SJ, Daejeon KR, Kim DH, and Anyang-si KR: United States Patent No. US 2018 / 0148801 A1 WIPO: World Intellectual Property Organization.
55. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF, Keshavarzian A, Shannon KM, Krajmalnik-Brown R, Wittung-Stafshede P, Knight R and Mazmanian SK: Gut Microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell Elsevier Inc 2016; 167: 1469-80.
56. Sarkar A: Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends Neurosci 2016; 39: 763-81.
57. Allen AP: *Bifidobacterium longum* 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. Transl Psychiatry 2016; 6: e939.
58. Slykerman RF: Effect of *Lactobacillus rhamnosus* HN001 in pregnancy on postpartum symptoms of depression and anxiety: a randomised double-blind placebocontrolled trial. EBioMedicine 2017; 24: 159-65.
59. Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C and Gil A: Probiotic mechanisms of action. Ann Nutr Metab 2012; 61: 160-74.
60. Gogineni VK, Morrow LE and Malesker MA: Probiotics: mechanisms of action and clinical applications. J Prob Health 2013; 1: 101.
61. Tysk C, Lindberg E and Järnerot G: Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins: A study of heritability and the influence of smoking. Gut 1988; 29: 990-96.
62. Kruis W, Schutz E, Fric P, Fixa B, Judmaier G and Stolte M: Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment Pharmac The 1997; 11: 853-58.
63. Husebye E, Hellström PM, Sundler F, Chen J and Midtvedt T: Influence of microbial species on small intestinal myoelectric activity and transit in germfree rats. Am J Physiol Gastrointest Liver Physiol 2001; 280: G368-80.
64. Niedzielin K and Kordecki H: Therapeutic usefulness of "ProViva" solution in the treatment of irritable bowel syndrome and hemorrhoids. Presented at the Symposium of Gastroenterology, Heiligenstadt, Germany 1996.
65. Aiba Y, Suzuki N, Kabir AM, Takagi A and Koga Y: Lactic acid mediated suppression of *Helicobacter pylori* by the oral administration of *Lactobacillus salivarius* as a probiotic in a genotobiotic murine model. Am. J. Gastroenterol 1998; 93: 2097-01.
66. Loguercio C, Del Vecchio Blanco C and Coltorti M: *Enterococcus* lactic acid bacteria strain SF68 and lactulose in hepatic encephalopathy: a controlled study. J Int Med Res 1987; 15: 335-43.
67. Global Statistics. https://www.hiv.gov/hiv-basics/over view/ data-and-trends/global-statistics
68. Villar-Garc´ıa J, Hern´andez JJ and G¨uerri-Fern´andez R: Effect of probiotics (*Saccharomyces boulardii*) on microbial translocation and inflammation in HIV-treated patients: a double-blind, randomized, placebo-controlled trial. Journal of Acquired Immune Deficiency Syndromes 2015; 68(3): 256-63.
69. Whaling MA, Luginaah I and Reid G: Perceptions about probiotic yogurt for health and nutrition in the context of HIV/AIDS inMwanza, Tanzania. Journal of Health, Population and Nutrition 2012; 30(1): 31-40.
70. Anukam KC, Osazuwa EO, Osadolor HB, Bruce AW and Reid G: Yogurt containing probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 helps resolve moderate diarrhea and increases CD4 count in HIV/AIDS patients. Journal of Clinical Gastroenterology 2008; 42(3): 239-43.
71. Salari P, Nikfar S and Abdollahi M: A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. Inflammation & Allergy - Drug Targets 2012; 11(1): 3-14.
72. Carter GM, Esmaeili A and Shah H: Probiotics in human immunodeficiency virus infection: a systematic review and evidence synthesis of benefits and risks. Open Forum Infectious Diseases 2016; 3(4): ofw164.
73. Hummelen R, Changalucha J and Butamanya NL: Effect of 25 weeks probiotic supplementation on immune function of HIV patients. Gut Microbes 2011; 2(2): 80-85.
74. Balducci L: Aging, frailty, and chemotherapy. Cancer Control 2007; 14(1): 7-12.

75. Lee JW, Shin JG, Kim EH, Kang HE and Yim IB: Immunomodulatory and antitumor effects *in-vivo* by the cytoplasmic fraction of *Lactobacillus casei* and *Bifidobacterium longum*. Journal of Veterinary Science 2004; 5: 41-48.
76. Russo F, Orlando A, Linsalata M, Cavallini A, and Messa C: Effects of *Lactobacillus rhamnosus* GG on the cell growth and polyamine metabolism in HGC-27 human gastric cancer cells. Nutrition and Cancer 2007; 59(1): 106-14.
77. Orlando A, Refolo MG and Messa C: Antiproliferative and proapoptotic effects of viable or heat-killed *Lactobacillus paracasei* IMPC2.1 and *Lactobacillus rhamnosus* GG in HGC- 27 gastric and DLD-1 colon cell lines. Nutrition and Cancer 2012; 64(7): 1103-11.
78. Kim Y, Lee D, and Kim D: Inhibition of proliferation in colon cancer cell lines and harmful enzyme activity of colon bacteria by *Bifidobacterium adolescentis* SPM0212. Archives of Pharmacal Research 2008; 31(4): 468-73.
79. Kim Y, Oh S, Yun HS, Oh S and Kim SH: Cell-bound exopolysaccharide from probiotic bacteria induces autophagic cell death of tumor cells. Letters in Applied Microbiology 2010; 51(2): 123-30.
80. Borowicki A, Michelmann A and Stein K: Fermented wheat aleurone enriched with probiotic strains LGG and Bb12 modulate markers of tumor progression in human colon cells. Nutrition and Cancer 2011; 63(1): 151-60.
81. Stein K, Borowicki A and Scharlau D: Effects of symbiotic fermentation products on primary chemo-prevention in human colon cells. The Journal of Nutritional Biochemistry 2012; 23(7): 777-84.
82. Cousin FJ, Jouan-Lanhouet S, Dimanche-Boitrel MT, Corcos L, and Jan G: Milk fermented by *Propionibacterium freudenreichii* induces apoptosis of HGT-1 human gastric cancer cells. PLoS One 2012; 7(3): e39812.
83. Cha M, Lee D and An H: Antiviral activity of *Bifidobacterium adolescentis* SPM1005-A on human papillomavirus type 16. BMC Medicine 2012; 10(1): 72.
84. Azam R, Ghafouri-Fard S and Tabrizi M: *Lactobacillus acidophilus* and *Lactobacillus crispatus* culture supernatants downregulate the expression of cancer-testis genes in the MDA-MB-231 cell line. Asian Pacific Journal of Cancer Prevention 2014; 15(10): 4255-59.
85. Ghoneumand M and Gimzewski J: Apoptotic effect of a novel kefir product, PFT, on multidrug-resistant myeloid leukemia cells *via* a hole-piercing mechanism. International Journal of Oncology 2014; 44(3): 830-37.
86. Toi M, Hirota S and Tomotaki A: Probiotic beverage with soy isoflavone consumption for breast cancer prevention: A case-control study. Current Nutrition and Food Science 2013; 9(3): 194-00.
87. Ma EL, Choi YJ, Choi J, Pothoulakis C, Rhee SH and Im E: The anticancer effect of probiotic *Bacillus polyfermenticus* on human colon cancer cells is mediated through ErbB2 and ErbB3 inhibition. International Journal of Cancer 2010; 127(4): 780-90.
88. Nami Y, Haghshenas B, Haghshenas M, Abdullah N and Yari Khosroushahi A: The Prophylactic effect of probiotic *Enterococcus lactis* IW5 against different human cancer cells. Frontiers in Microbiology 2015; 6: 1317.

How to cite this article:
Chowdhury R and Chakraborty T: A quest for better probiotic delivery and frontiers of probiotic application in medical science: a critical review. Int J Pharm Sci & Res 2019; 10(9): 3993-05. doi: 10.13040/IJPSR.0975-8232.10(9).3993-05.