

Exploring Role of Probiotics in Clinical Practice

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Abstract

The concept of probiotics, which emerged in ancient times is a rapidly advancing field. Probiotics have impact on human health. Probiotic bacteria are used to treat or prevent a broad range of human diseases, conditions and syndromes. Probiotics are effective in treatment and prevention of acute diarrhea and antibiotic induced diarrhea. Potential applications of probiotics are for treatment and prevention of relapses of Crohn disease, ulcerative colitis, irritable bowel syndrome. Probiotics may be useful for prevention of respiratory infections in children, dental caries, allergic diseases. They are valuable in gynaecology in bacterial vaginosis, vulvovaginal candidiasis and urogenital infections. Areas of future interest for application of probiotics include colon and bladder cancer, diabetes and rheumatoid arthritis.

Keywords: Probiotics; Lactobacillus; Gastrointestinal infectious; Urogenital infections; Health care.

Introduction

The term probiotic was derived from the Greek word, meaning supporting life or favouring life. The concept of probiotics is very ancient. Mention of cultured dairy products is found in the Bible and the sacred scriptures of the Hindus. The benefits of probiotics have been recognized and explored for over a century. The pioneer research of Metchnikoff's theory of longevity was converted into commercial reality by Shirota and Kellogg in 1930.

The aim of this article is to pay tribute to pioneers in the field and to provide recent knowledge in the field of probiotics. History of probiotics is highlighted. The article will

focus on types of bacteria in probiotics and their mechanism of action. We capture the impact of probiotics in clinical practice, including gynaecology and women's health.

What are Probiotics

Soured milk and cultured dairy products such as kefir, koumiss, leben and dahi were often used therapeutically before the existence of microorganisms was recognized. The use of microorganism in food fermentation is one of the oldest methods for producing and preserving food.[1]

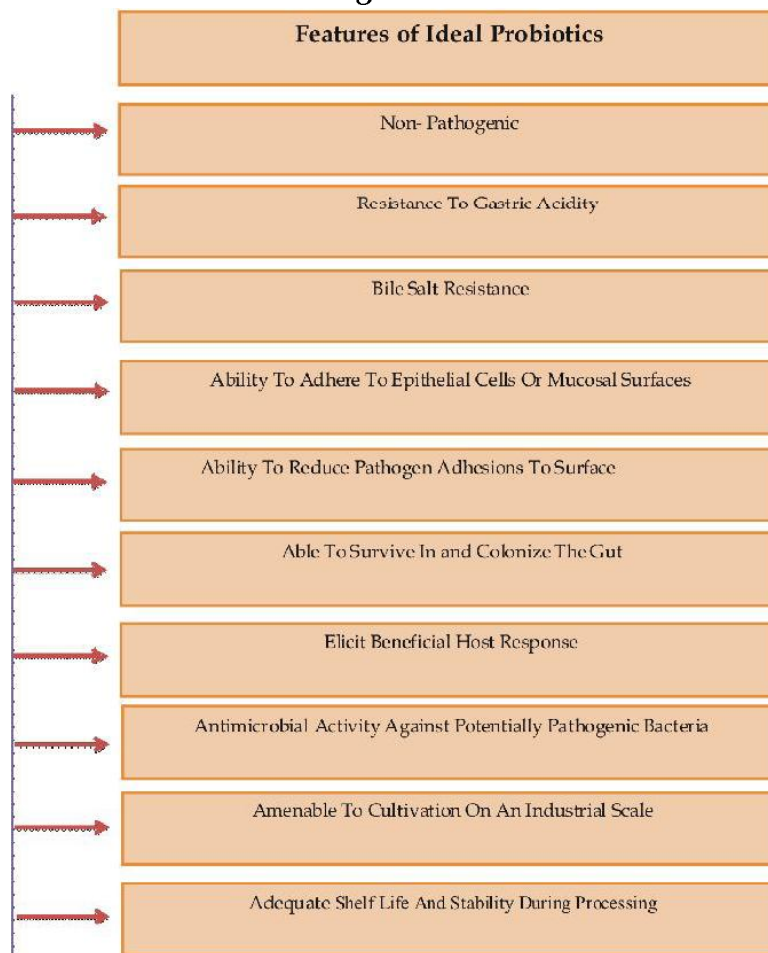
The rationale for using probiotics is that the body contains a miniature ecology of a number of bacteria known as natural flora. The flora can be thrown out of balance by a wide range of circumstances including the use of antibiotics or other drugs, excess alcohol, stress, disease, exposure to toxic substances, and even the use of antibacterial soap. In these circumstances, symbiotic bacteria decrease in number and allow to thrive pathogenic organisms which are detrimental to health. Probiotics are defined as live microorganisms which when administered in adequate

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Figure 1

amounts, confer a beneficial health effect on the host.[1]

The probiotics that are marketed as nutritional supplements and used in foods, such as yogurt, are principally the bifidobacteria species and the lactobacillus species. The effectiveness of probiotics is related to their ability to survive in the acidic environment of the stomach and the alkaline conditions in the duodenum, as well as their ability to adhere to the intestinal mucosa of the colon and to colonize the colon.[1]

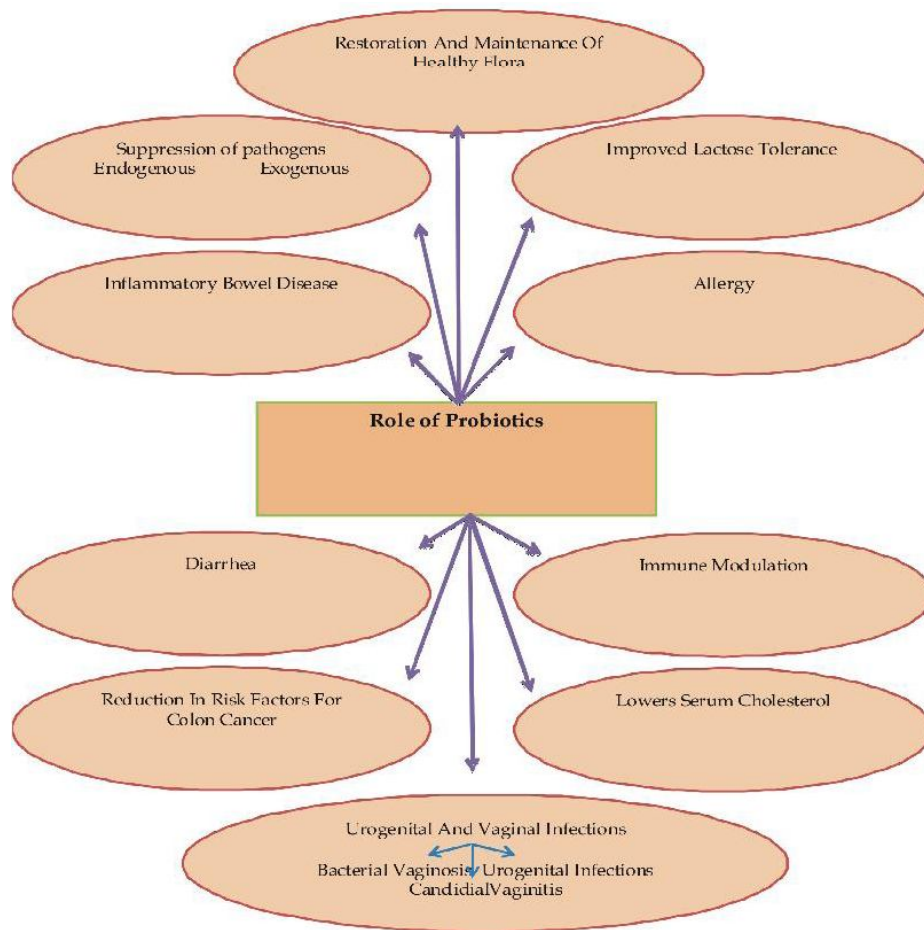
Probiotics help to provide optimum balance in the intestines. Probiotics species competitively block toxic substances and growth of unwanted bacteria and yeast species while they compete for the space. The microorganisms need to be alive when they are consumed and therefore maintaining suitable conditions for their storage and transport

before consumption is important. Probiotics may have antimicrobial, immunomodulatory, [1] anticarcinogenic, antiallergic, antidiarrheal and antioxidant properties. The various mechanisms include chelation of metallic ions, scavenging of reactive oxygen species, and reduction of bacterial activity.[1]

Some of the characteristics are considered essential for a probiotic to have therapeutic effects. These are:

- 1) gastric acid and bile salt stability;
- 2) an ability to adhere to the intestinal mucosa; and
- 3) an ability to colonise the intestinal tract (at least temporarily).

Before prescribing any probiotic supplement or food, it is imperative to ensure that the bacterial strains contained in the product have these three vital qualities. If not, it is wise to

Figure 2:Role of Probiotics

prescribe one that does. Other vital characteristics include the ability to produce antimicrobial compounds and to directly antagonise more pathogenic organisms. Additionally, the anti-microbial compounds produced should have selective activity, so that they inhibit the growth of pathogenic bacteria, but not beneficial species.[2]

Types of Bacteria in Probiotics

Lactobacillus acidophilus NCFM produces antimicrobial substances that inhibit the growth of some beneficial species of bacteria, including *L. fermentum*, *L. delbrueckii* ssp. *lactis*, and *L. delbrueckii* ssp. *bulgaricus*, whilst having no effect on pathogens. Whereas *L. rhamnosus* GG and *L. johnsonii* La1 produce compounds that only inhibit the growth of potentially pathogenic bacteria, not beneficial ones. Another important probiotic characteristic, is the ability of the strain to

beneficially alter the composition of the GIT flora when consumed – both reducing numbers of potentially pathogenic organisms and increasing numbers of beneficial organisms.[2]

Clinical Utility of Probiotics

Uses in Gastrointestinal Diseases

Neonates

Intestinal infections in newborn children are common, and in developing countries diarrhea is a prime cause of morbidity and mortality. Necrotizing enterocolitis is one devastating intestinal disorder that a preterm infant may face within a neonatal intensive care unit. If non pathogens, such as lactobacilli and bifidobacteria, colonize the intestine, or if breast milk rather than formula is used, the incidence of necrotizing enterocolitis has been reported to fall.[3]

The immune response within the gastrointestinal tract is a fine balance between the release of proinflammatory (e.g., interleukin-1, -6, and -8 and tumor necrosis factor) and anti-inflammatory (e.g., interleukin-1RA, -4, and -10) cytokines. In a review on mucosal immunity starting at birth, Walker reported a correlation between a normal gut microbiota and protection against various infections. This is an important observation because it supports the concept of early intestinal colonization with organisms such as lactobacilli and bifidobacteria and possibly subsequent protection from necrotizing enterocolitis and other diseases.[3]

At the least, probiotics provide a safe and potentially beneficial remedy, especially when delivered in milk, which provides the child with nutrition and a means to overcome adverse effects of fluid loss. The strongest evidence of a beneficial effect of probiotics has been established with *L. rhamnosus* GG and *B. lactis* BB-12 for prevention and *L. reuteri* SD2222 for treatment. There is sufficient evidence to recommend use of at least one probiotic strain, *L. rhamnosus* GG, in capsule or milk form, to treat acute diarrhea in children, in combination with standard oral rehydration.[3]

Irritable Bowel Syndrome

Probiotic use in patients suffering from inflammatory bowel disease (IBD) is now quite common, with numerous published clinical trials. Studies have shown that probiotic intervention has helped to decrease immunological disturbances, modify disease activity, and assist in the normalization of increased intestinal permeability.[4]

Treatment and Prevention of Relapses of Inflammatory Bowel Disease.

One of the major potential applications of probiotics is for the treatment and prevention of relapses of Crohn disease, ulcerative colitis, and irritable bowel syndrome.

There have been reports of beneficial effects

for inflammatory bowel disease that resulted from the administration of *Lactobacillus salivarius*, *Escherichia coli* strain Nissle, *S. boulardii*, and VSL#3 (VSL pharmaceuticals).[5]

Lactose Malabsorption

A large number of people, as they age, experience a decline in the level of lactase (Beta galactosidase) in the intestinal brush border mucosa. Resulting in flatus, bloating, abdominal cramps, and moderate-to-severe (watery) diarrhea. During the fermentative process involved in the production of yogurt, lactase is produced, which can exert its influence in the intestinal tract. The delivery of lactase to the intestine via the consumption of lactase-producing probiotics is a practical approach for treatment of lactose malabsorption.[5]

An Emerging Trend of High-Dose Probiotic Use in Clinical Practice

The use of probiotics as bio-therapeutic agents is common place. These probiotics are typically delivered in relatively low-dose functional foods (primarily yogurts) providing up to a few billion colony forming units (CFU); or in modest doses, in the form of dietary supplements of 5-25 billion CFU. Over the past several years, a trend has emerged in which much higher doses of probiotics are being used in both clinical practice and research.[4]

Not surprisingly, the initial focus of the clinical research on high-dose probiotics has been on functional GI disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and antibiotic-associated diarrhea (AAD). These conditions represent extreme examples of dysbiosis and dysfunction within the mucosal immune system of the gut; a system which is integrally associated with the microflora of the gut lumen. Although supplemental probiotics are only temporary members of the intestinal microbiota (perhaps 1-2 weeks), the introduction of large quantities of probiotics

may sufficiently alter this environment allowing the probiotic to act as a potent bio-therapeutic agents in a manner that a lower dose would not.[4]

Antibiotic Induced Diarrhoea

It is well known that antibiotic therapy can severely disrupt the gut microbial ecology. Taking a probiotic during antibiotic therapy can often help preserve beneficial flora and improve stool consistency and frequency.[4]

The Role of Probiotics in Allergic Disorders

The interest in probiotic therapeutic potential in allergic disorders stemmed from the fact that they have been shown to reduce inflammatory cytokines and improve intestinal permeability in vitro. Such effects would be desirable in treating allergic disorders. Therefore, several studies have been designed to examine the efficacy of probiotics in many allergic conditions, such as eczema, allergic rhinitis, asthma, food allergies and in children with atopic conditions such as atopic dermatitis.[6]

Probiotics in Oral Health

Probiotics Impact on Oral Health Issues

Oral administration of probiotics has a direct impact on dental caries. *Lactobacillus rhamnosus* and *Lactobacillus casei* have proved their potential to hamper growth of oral streptococci, chronic periodontitis can also benefit from probiotics. Antagonistic interactions can regulate periodontal pathogens. Krasse have reported that application of *L. reuteri* can decrease gum bleeding and gingivitis. *Candida albicans*, yeast is among the most common infectious agents in the mouth, especially amongst the elder and patients with compromised immunity. Elahi *et al*, showed that application of *L. acidophilus* and *L. fermentum* resulted in decline of *C. albicans* in mice. Natakka *et al*, registered a reduction in *C. albicans* after administering probiotics chesse containing *L. rhamnosus* to the elderly. Classical probiotic

strains include *Lactobacillus* and *Bifidobacterium* species which have positive probiotic impact on the oral cavity. Genetically modified probiotic strains involve the administration of live microorganisms with their genes modified.[7]

Probiotics in Cancer

The ability of lactobacilli and bifidobacteria to modify the gut microbiota and reduce the risk of cancer is in part due to their ability to decrease β -glucuronidase and carcinogen levels. Cancer recurrences at other sites, such as the urinary bladder, also appear to be reduced by intestinal instillation of probiotics, including *L. casei* shirota (the strain present in Yakult, a Japanese milk-based drink taken by an estimated 26 million people every day).[3]

Role of Probiotics in Gynaecology

Bacterial Vaginosis

Many women with BV are asymptomatic yet are at risk of more serious complications such as endometriosis, pelvic inflammatory disease and complications of pregnancy including preterm labour. Oral and vaginal administration of lactobacilli can eradicate asymptomatic and symptomatic Bacterial Vaginosis. Oral administration of *Lactobacillus acidophilus* and yogurt has been used in the prevention and therapy of candidal vaginitis, although no efficacy data have yet been generated. The necessity for the lactobacilli to produce hydrogen peroxide has been proposed, but given that these microorganisms are more prone to being killed by spermicides, the combination of 2 or more strains, one of which produces hydrogen peroxide and others which resists spermicidal killing, may prove to be more therapeutic. Probiotic may be important for reducing the preterm birth rate in pregnant women. Probiotics can safely used before pregnancy or in the first trimester. It may be used as in adjunctive to therapy in the second trimester avoiding potential side effects. The optimal treatment and prophylaxis against BV should preferably be natural, non-

toxic for humans or healthy vaginal microflora, biodegradable and cost effective. [8]

Vulvovaginal Candidiasis

The vaginal microbiota is one of the first lines of defense against vulvovaginal candidiasis (VVC). The low p^H is considered a result of microbial metabolic products (mostly lactic acid) of glycogen, which is produced by vaginal epithelial cells. During menses, the composition of the vaginal microbiota is destabilized and it is at that time that probiotic lactobacilli may have a role to play in maintenance of the barrier to *C. albicans* infection. [9]

The recurrent use of antifungal agents for vulvovaginal candidiasis is a matter of concern for the proliferation of drug-resistant strains of yeast. Probiotic treatments may be an alternative or adjunct to antimicrobial drug use. The pH of the media was decreased in the presence of the lactobacilli, which is also known to be inhibitory to *C. albicans*. [9]

VVC symptoms emerge during times of increased estrogen levels in the vaginal tract and suggests a mechanism by which some probiotic lactobacilli can be protective against VVC. From a regulatory science viewpoint, we suggest that future probiotic bacterial strains be selected for their ability to limit 17β -estradiol-induced growth and hyphal germination by *C. albicans*. [9]

HIV

Among people living with HIV, the gut is one of the most severely affected sites. 80% of entire cell population resides in the gut, the gut of HIV patients is the centre of many problem. Their intestinal barrier is severely damaged, causing influx of bacterial products into blood stream, poor uptake of nutrients and chronic diarrhea. This results in systemic inflammation, HIV replication and faster progression towards AIDS whether modifying the intestinal microflora may result in reduced immune activation and increased CD4 count

is a link that warrants further investigations.

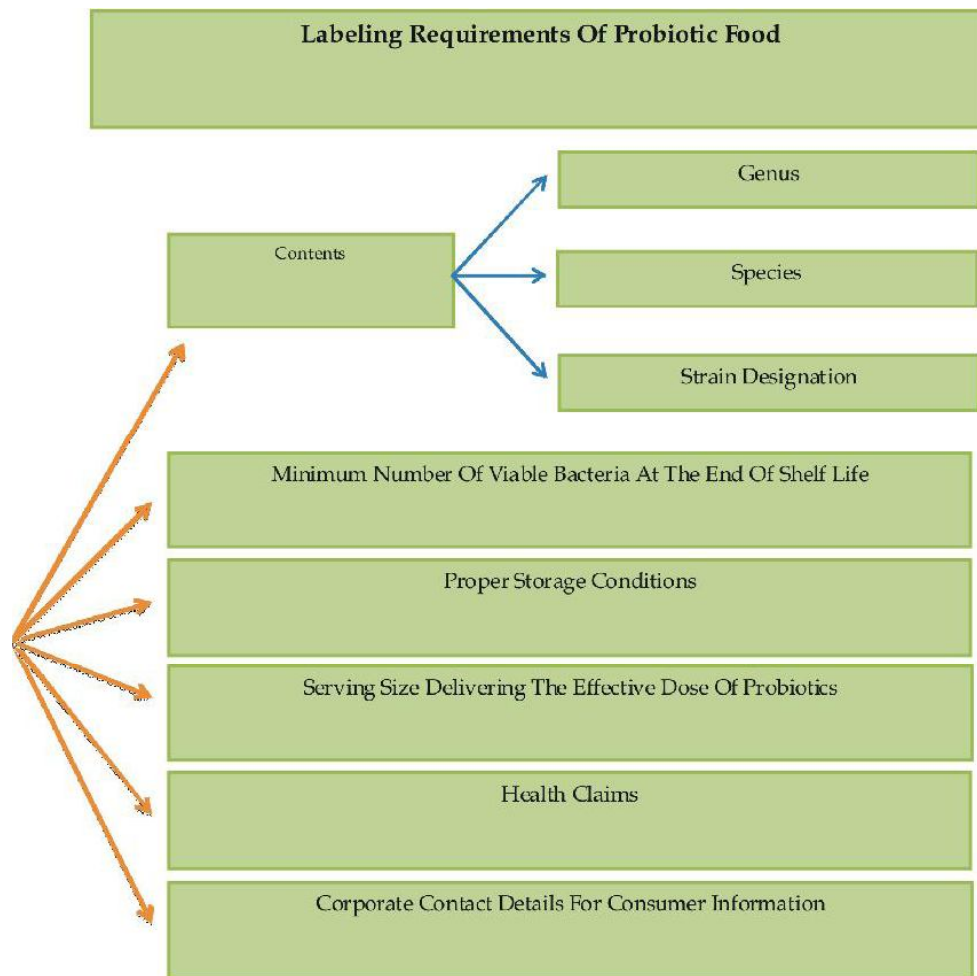
The supplementation of lactobacillus in a food based product or a capsule provides a potential way to improve the vaginal flora. Lactobacillus strains have been shown in vitro to directly inhibit the growth of various vaginal pathogens such as *Gardnella vaginalis*, *Neisseria gonorrhoea* and HIV. They also compete for adhesion sites, stimulate the local antimicrobial immune response and lower the p^H . [10]

Urogenital Infections

The use of probiotics, especially lactobacilli, has been considered for the prevention of UTIs. Since lactobacilli dominate the urogenital flora of healthy premenopausal women, it has been suggested that restoration of the urogenital flora, which is dominated by uropathogens, with lactobacilli may protect against UTIs. [11]

Many clinical trials in women with UTIs have been carried out to assess the effectiveness and safety of probiotics for prophylaxis against uropathogens. Most of them had encouraging findings for some specific strains of lactobacilli. *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 (previously called *L. fermentum* RC-14) seemed to be the most effective among the studied lactobacilli for the prevention of UTIs. The evidence from the available studies suggests that probiotics can be beneficial for preventing recurrent UTIs in women; they also have a good safety profile. [11]

Antimicrobial treatment of urogenital infections are not always effective and problems arise due to bacterial infections, yeast resistance and recurrent infections as well as side effects related to their use. Alternative remedies are of interest to patients as well as doctors. Recurrences are due to antimicrobials failing to eradicate pathogens, perhaps due to resistance or the virulent organisms reinhabit the vagina from the gut or the partner. Recurrent infection may also be due to the elimination of the most common organisms in the vagina by antimicrobial therapy, increasing susceptibility to

Figure 3

recolonization by pathogens.[10]

CIN

The relationship between BV and cervical dysplasia and Ca is not consistent. The possible role of B.V. in the etiology of CIN is the failure to control STI particularly oncogenic HPV. It has been suggested that BV with anaerobes are capable of producing carcinogenic substances called nitrosamines.

Food Rich in Probiotics

With the increasing evidence that some bacteria can be beneficial to human health and metabolism, the interest in foods containing live bacteria has increased and today food manufactures are adding beneficial bacteria to a wide variety of foods and beverages.[12]

No. of carriers for probiotics have been examined recently including mayonnaise, edible spreads and meat in addition to other products of dairy origin; Probiotic organisms are available commercially in milk, sour milk, fruit juices, ice-cream ,oat based products. One of the earliest probiotic effects to be exploited for human benefit is the production of lactic acid as a normal end product of fermentation by various lactic acid bacteria including Lactobacillus. The antimicrobial action of lactic acid has long been used for food preservation.[10]

Preparations of Probiotics

Typical doses of probiotics range from one to ten billion colony forming units (CFU), to be taken a few times a week, to maintain their effect on the microecology. The microorganisms

need to be alive when they are consumed and therefore maintaining suitable conditions for their storage and transport before consumption is important.[1] Insertion of lactobacilli into the vagina via a pessary or capsule is an effective means of boosting content of the flora and overcoming some pathogens or reducing their ability to dominate. This seems to be true for treatment of BV and possibly UTI pathogens. The dried lactobacilli used in vaginal suppositories appear to be capable of hydrating from the capsule and interfering with pathogenic organisms. Oral dosage seems to require around 10^9 viable bacteria once or twice weekly, although a once-per-day vaginal protocol for 3 days might initially be required to displace large pathogen biofilms in the urogenital tract.[13] Natural antimicrobials from *Lactobacillus* spp. can be further optimized using the multiple hurdle approach. Hurdle technology is the combination of different stress factors such as chemical or biological preservatives, low pH, temperature, oxidative compounds and competitive microorganisms to achieve a synergistic or additive effects to control pathogenic bacteria.[13]

Labelling of Probiotics

It is essential to label the probiotic product precisely. The market labels should contain the name of the used strain, the number of viable bacteria and indications for treatment. Sufficient number of probiotic cells must survive through the shelf life of product.

Side Effects

Possible Negative Effects of Probiotics

Annually over one billion doses of probiotics are administered worldwide, those administered for urogenital health are well tolerated. More clinical trials are to be conducted for confirmation of its safe therapeutic use. Probiotics should not be used as replacement option. In normal healthy persons, probiotics when taken in recommended doses does not cause any

significant side effects. In case of people having an underlying disease or a compromised immune system, probiotics can cause potential health problems. Probiotics may disturb the normal metabolic processes and autoimmune responses of the body. According to medical studies conducted, there is a possibility that probiotics may interact with immunosuppressive drugs, leading to life threatening conditions. Hence those who are on immunosuppressive medications should strictly avoid probiotics. Effects of particular probiotic vary from those of another. Hence, while opting for a probiotic, it is important to select the specific probiotic strain.[8]

Discussion

As health care providers, we are striving for disease prevention and probiotics lead us to believe, they will aid in this medical effort. *Probiotics are not magic bullets* but evidence is accumulating that the use of probiotic strains will help restore and maintain urogenital and intestinal health. Intake of scientifically selected probiotics would provide natural, safe, and effective means of regulating the fluctuating vaginal flora and thereby lower the risk of infection in healthy and sick women. Probiotics are important tools in the therapeutic procedure and essential component supporting the pharmacological treatment, especially along with rapid increase of antibiotic treatment of bacteria. It is essential to know the potential side effects such as systemic infections, overstimulation of immunological systems or gene transfer.

The non-pathogenic organisms used as probiotics consist of a wide variety of species and subspecies, and the ability to adhere, colonize and modulate the human gastrointestinal system is not a universal property. *Lactobacillus* and *Bifidobacterium* are the main probiotic groups. Health effects imparted by probiotic bacteria are very strain specific, therefore there is no universal strain that would provide all proposed benefits, not even strains of the same species. It is critically

important that strains are characterized and tested clinically using delivery system of choice.

The viability of probiotics is a key parameter for developing probiotic food products. New technologies have been developed to enable high cell yield at large scale and ensure probiotic stability for a long period in food. Various food matrices, dairy and non-dairy, have been used with probiotics with different technologies, such as microencapsulation, cell immobilization and continuous fermentation. The probiotics will become an important and viable ingredients in functional foods, expanding the probiotic application outside the pharmaceutical and supplement industries.

More efficient technologies could lead to greater product efficacy and strain diversification. Some authors have presented developments in fermentation technologies for producing probiotic bacteria as well potential new approaches for enhancing the performance of these organisms during fermentation, downstream processing, and utilization in commercial products, and for improving functionality in the gut.

Human testing will be vital not only to fulfil the requirements for strain to be called probiotic, but to increase our understanding of how products work. Applications in the field of cancer, cardiovascular disease, inflammation, allergy and infection are currently the main target areas with potential to benefit large numbers of people.

Future applications include the treatment of rheumatoid arthritis, treatment of irritable bowel syndrome, cancer prevention, prevention of ethanol-induced liver disease, treatment of diabetes, and prevention or treatment of graft versus-host disease. The use of probiotics in medical practice is rapidly increasing, as are studies that demonstrate the efficacy of probiotics. Overall, probiotics appear to be here to stay as part of the physician's armamentarium for the prevention and treatment of disease.

The emergence of new molecular,

microscopic, nanoscale and imaging technologies will make it feasible to see in real time how probiotic (and indeed indigenous) bacteria influence the host. This will keep human regain their health when adversely affected by pathogenic microbial damage, antimicrobial treatments and other threats. Probiotics is the concept where science and commerce need to meet.

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