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PROBIOTICS, AN APPROACH TOWARDS MODERN MEDICATION

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ABSTRACT

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses. SARS-CoV-2 is a beta coronavirus, a genus that includes several coronaviruses (SARS-CoV, MERS-CoV, bat SARS-like CoV, and others) isolated from humans, bats, camels, civets, and other animals. Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) is the pathogenic agent that causes the disease COVID-19. SARS-CoV-2 is thought to have emerged from an animal source, most likely a bat, and subsequently spread to humans. While genetically closely related viruses have been isolated from Rhinolophus bats, the exact source of SARS-CoV-2 and its route of introduction into the human population have not been established. Monitoring animal infections is imperative to better understanding their epidemiological significance for animal health, biodiversity, and human health. According to evidence from risk assessments, epidemiological investigations, and experimental studies, animals play no significant role in the spread of SARS-CoV-2, which is sustained by human-to-human transmission. The possibility of Coronavirus testing by veterinary labs was considered after the Iowa State veterinary lab discovered the COVID-19 virus has a similar DNA testing process to porcine epidemic diarrhea virus (PED). PED is another form of coronavirus that killed many piglets in 2013 and was unresponsive to treatment. Several vet labs optimized their equipment and processes to test for PED, helping them determine that older pigs could recover and develop immunity against the virus. Those same labs are still set up for coronavirus testing. We in Dubai Safari Park, particularly within the laboratory Veterinary Hospital, are conducting RT-PCR analysis to test diverse animal species including non-human primates, Carnivores, small mammals, and Ungulates. Even though none of our animals show any respiratory signs, we have conducted this study to ensure that our animal collection is healthy and free of SARS-COV-2.

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INTRODUCTION

The word Probiotics is derived from two words, pro means for and bios means life. Stillwell and Lilly proposed the name “probiotics” in 1965. Later, the concept of probiotics was substantially described by Metchnikoff in 1907. Earlier, the term ‘probiotics’ was considered as an anonym of term ‘antibiotic’. Various published studies documented these beneficial microorganisms as health friendly bacteria while supplemented properly as a food and medicines which leads confer health benefits (Araya *et al.*, 2006; Rijkers *et al.*, 2011; Hill *et al.*, 2014). Microorganisms live in the gut of humans, following

symbiotic relationships.

The utilization of yogurt continuously for longer time helps in preventing fouling of large intestine, thus helping to live a longer and healthier life. Probiotics were initially used by Kollath in 1953 in malnourished patients to restore health as inorganic and organic supplements. Probiotics, when supplemented after utilization of antibiotics, help in restoring gut flora. World Health Organization in 2001 revealed that probiotics when taken in appropriate amounts provide health benefits (Jorgen, 2012). There are food components that are nonviable and give health benefits when supplemented appropriately by modulating gut microbiota and are termed as prebiotics by FAO in 2007.

Human intestinal flora is not completely renowned till now (Relman *et al*., 2001) but the role of microorganisms is well known and appreciated in providing health benefits to human body. The numbers of microorganisms in the human body are ten times more than the number of cells in human body. Scientists came to know in the last few years that the human body contains microorganisms ten times more in number than total human body cells. These microorganisms contain 150 times more genes than the human genome (Savage, 1977).

Probiotics are found in fermented foods and cultured milk and infant food is prepared using probiotics. As it is known for a lot of time that bifidobacterial and lactic acid bacteria don't cause any harm, so in Europe they have a status of Qualified Presumption of Safety (QPS) while generally regarded as safe (GRAS) in USA. Policies are being implemented by Malaysian government in order to encourage natural and healthy lifestyle, promoting food products similar to conventional food as well as carry bioactive microorganisms in turn leading to health benefits (Stanton *et al.,* 2011; Arora *et al*., 2013). Some bacterial species that naturally inhabit intestinal tract includes *Saccharomyces*, *Lactobacillus*, *Enterococcus*, *Bifidobacterium*, *Pediococcus*, *Streptococcus*, *Leuconostoc*, *Eustrachia* and *Bacillus*. Species belonging to *Lactobacillus* and *Bifidobacterium* are being used by humans for a long time.

CLASSIFICATION OF PROBIOTICS

Lactobacillus Species

L. casei, L. rhamnosus, L. acidophilus, L. gasseri, L. plantarum reuteri, L. crispatus, L. johnsonii, L. paracasei, (Kailasapathy and Chin, 2000; Ishibashi and Yamazaki, 2001).

Bifidobacterium Species

B. adolescentis, B. animalis, B. bifidum, B. infantis, B. breve, B. longum and *B. lactis* (Bottacini *et al.,* 2014).

Lactic acid Bacteria

Enterococcus aecium, E. faecalis, Leuconostoc mesenteroides, L. lactis, Sporolactobacillus inulinis, Pediococcus acidilactici and *Streptococcus thermophilus.*

Non-Lactic acid Bacteria

Escherichia coli, Bacillus cereus, Propionibacterium freudenreichii, Saccharomyces cerevisiae and *S. boulardi* (Ramos *et al*., 2022).

MECHANISM OF ACTION

Mechanisms by which probiotics act vary from strain to strain. Each strain has its own mechanism by which it provides health benefits while sometimes different mechanisms act in coordination with each other for providing health benefits. Epithelial cells of intestine are affected by probiotics organisms that are shown by their mechanism of action.

1. Various physical barriers are produced that resist the entry of pathogenic bacteria in epithelial cells.
2. It enables the production of mucus barrier through goblet cells.
3. Strain of some probiotics enhances intercellular integrity of apical tight junctions thus maintaining permeability of intestine. Hence intestinal wall become impermeable to pathogenic bacteria through epithelial cells.
4. Bacteriocins are antimicrobial substance that are produced by some strain of probiotics (Cotter *et al*., 2005)
5. Some antimicrobial substance produces metabolites such as lactic acid and acetic acid that kill pathogens (Servin, 2004).
6. Some strains of probiotic microbes work in increasing innate immune system.

SELECTION CRITERIA OF PROBIOTICS

A major problem while selecting suitable strain of probiotics is safety concern. *Bifidobacterium* and *Lactobacillus* are considered safe as being in use for a lot of time. Safety assessment must be performed while selecting any other strain as a probiotic other than *Bifidobacterium* and *lactobacillus* (European Food Safety Authority, 2007; Leuschner *et al*., 2010).

Various factors should be considered while selecting microorganisms to be used as probiotics.

1. The risk of strain to produce any disease to host should be investigated. Before recommending any probiotic the metabolic activity and toxicity of host should be recommended. (Ishibashi and Yamazaki, 2001).
2. If probiotics are to be stored for later use then optimum required conditions and viability of strain should be investigated (Shi *et al*., 2010).
3. For the proper functioning in intestine, it is important for the strain to survive the gastric pH. Because strain can only provide beneficial effects if it is able to survive and tolerate bile salt and gastric juice (Kailasapathy and Chin, 2000; Ishibashi and Yamazaki, 2001). For this purpose, while working in lab, the environmental conditions similar to the environment of stomach are provided in order to check that is strain able to tolerate gastric juice and bile secretions or not.
4. The retentiveness of strain in human gut is estimated by checking its adherence to epithelial cells (Ouwehand and Salminen, 2003; Forssten *et al*., 2011). The interaction of strain to indigenous microbiota and host should be checked.
5. It is required for strain to necessarily have bile salt hydrolase (BSH) activity.
6. Strain must possess antimicrobial activity to protect against pathogenic bacteria.

RECOMMENDED DOSE OF PROBIOTICS

Appropriate dose of probiotics is suggested for effectiveness. The units that are used for suggesting the dose of probiotics are CFU (Colony forming unit per gram of product). However, a lot of research is needed to explore the minimum dose that would be effective for the treatment.

Generally, the dose that is prescribed for treatment is 106CFU per gram or per ml of product.

HEALTH BENEFITS OF PROBIOTICS

It is well documented that probiotics play a role in treating a lot of diseases like cancer prevention, intestinal health improvement, orodental problems or hypercholesterolemia effectively (Kechagia *et al.,* 2013). However, there is need to identify these probiotics against different diseases except lactose intolerance, acute diarrhea or antibiotic associated diarrhea.

Probiotics as Cholesterol Lowering Substance

Multiple mechanisms of actions are suggested that probiotics undergo in order to lower serum cholesterol level. One study reveals that probiotics bind cholesterol to the surface of the cell (Shi *et al*., 2010). Another study shows that the formation of micelle for interrupting intestinal absorption. Microorganisms release Bile salt hydrolase (BSH) that functions in Bile salt deconjugation (Lambert *et al*., 2008).

BSH plays its role and makes bile salt less soluble and aids in excretion of free bile acid in stool. So, the level of cholesterol in serum is lowered because of de novo synthesis of bile acid in order to restore the excreted bile acid (Nguyen *et al*., 2007). Another researcher revealed that probiotics undergo this by co-precipitating by cholesterol (Zhang *et al*., 2008). Bile acid makes it easy for the cholesterol to the bacterial cell acting as a surfactant. As a result, my cholesterol is lowered. The attachment of the bacterial cell depends on bacterial growth (Shi *et al*., 2010)

Effect of Probiotics in Intestinal Disorder

Antibiotic associated diarrhea

When antibiotics are used for the treatment of various infectious diseases, in addition to pathogenic bacteria, normal intestinal flora got suppressed and as a result it may pose side effects like diarrhea. This suppression of normal intestinal micro flora led to the excessive growth of pathogenic flora which is a factor causing diarrhea.

The intensity of diarrhea may vary from mild to severe. Pseudo membranous colitis is a severe form of diarrhea. It was proved that *S. boulardii* and *L. rhamnosus* are useful for treating antibiotic associated diarrhea (McFarland, 2006; Sazawal *et al*., 2006). So, practitioners are using *S. boulardii* and *L. rhamnosus* in clinics but still research is required to know the minimum dose that would be effective for the treatment and the comparison is required to be done among different probiotics that could be used for treatment.

Infectious Diarrhea

The most known cause of diarrhea in children is the Rota virus. In vivo studies in rats showed that this occurs when a sufficient amount of normal flora is not present. Hence viral antigens got absorbed leading to infectious diarrhea in infants (Salminen *et al*., 1998). Probiotics usage proved to be beneficial for prevention as well as for treatment of infectious diarrhea. It was revealed by various studies that *L. casei, L. rhamnosus* and *L. reuteri* helps in reducing the interval of diarrhea induced by Rota virus (Shah, 2007; Isolauri, 2002).

It was reported that consumption of yogurt containing *L.*

casei by children of daycare shortens the duration of infectious diarrhea as compared to other children (Pedone, 1999). Research on animals reported the production of Bacteriocins due to consumption of probiotics that possess inhibitory effects on the pathogens present in intestine (Moslehi-Jenabian *et al*., 2011).

Inflammatory bowel disease

Inflammatory bowel disease is categorized as Crohn's disease (CD), Or Ulcerative colitis (UC) environmental factors or genetic predisposition can be a cause for Inflammatory Bowel Disease. It is an autoimmune disorder in which the immune system is disturbed leading to the body perceive food or good bacteria as pathogenic and start responding to them. So inflammatory bowel disease is caused when the balance between the microflora and the immune system is disturbed (Khor *et al*., 2011).

Patients of IBD show distinctive profile of microbiota (Hartman *et al*., 2009; Manichanh *et al*., 2006). It was revealed in a study that the disease and health control of micro flora is different (Morgan *et al*., 2012). Probiotics play an effective role in treating IBD. A study showed the presence of *L. salivarius* CECT 5713 and its anti-inflammatory effect in rats with Ulcerative colitis. This study showed that when probiotics were administered orally, they produce anti-inflammatory effects and work in reducing necrosis, thus improving the disease in unhealthy group (Peran *et al*., 2005). Another study revealed that when mouse with ulcerative colitis was supplemented with probiotic L. plantarum 91, the level of tumor necrosis factor - alpha (TNF-α) and Cyclooxygenase - 2 (COX-2) got reduced while anti-inflammatory cytokines like interleukin-4 (IL-4), interleukin-6 (IL-6) and interleukin -10 (IL-10) increases in production (Duary, 2011).

A clinical trial was conducted in which *L. rhamnosus* GG (LGG) was supplemented to 187 Ulcerative Colitis (UC) patients. 18×109 bacteria were supplemented per day, both with and without giving patients the standard treatment of mesalazine, whereas the dose of mesalazine was 2400mg per day. Results reveal the increase of relapse time in LGG as well as combination of LGG and mesalazine in comparison to the standard treatment (Zocco *et al*., 2006).

Lactose intolerance

Lactose intolerance is caused because of absence of an enzyme called beta-glactosidase. The function of this enzyme is to convert lactose present in milk into galactose and glucose. The absence of this enzyme leads to inability to metabolize lactose present in the milk and if anyone who is lactose intolerant uses any dairy product, develops a condition known as osmotic diarrhea. Microbes like *L. delbrueckii ssp. Bulgaricus* and *S. thermophiles* having increased betaglactosidase activity are known to be advantageous because it increases the metabolism of lactose (De-Vrese *et al*., 2001; Levri, 2005).

Role of Probiotics in Skin Problems

Probiotics have proved to be advantageous for the treatment of scars, wounds and atopic eczema. Probiotics also play a role in revitalizing skin. Weise *et al*. (2011) studied the effect of *Escherichia coli* Nussle 1917 (EcN, serotype O6: K5: H1) in mouse model (BALB/c mice) that was infected with dermatitis allergies and revealed that it starts producing cytokines and thus involves in modulating immune system (Weise *et al*., 2011). Another study was conducted which revealed that *B. bifidum, L. salivarius, L. acidophilus* and *L. casei* are beneficial in treating SCORAD. They proposed that these microbes have an effect on potential allergies as they are immunogenic (Yesilova *et al*., 2012).

Research showed that bacterial cells are effective for skin, but viable cells are not beneficial in treating skin problems. Different compounds of bacteria are effective e.g., lipoteichoic acid, hyaluronic acid, sphingomyelinase and peptidoglycan are known to be advantageous for skin (Lew and Liong, 2013). Isolauri *et al.* (2000) revealed that if mothers are supplemented with *L. rhamnosus*, the babies born to them have least risk of being susceptible to atopic eczema.

Probiotics use in Orodental Health

It is approved by different research that probiotics are useful for improving orodental health. It helps in improving oral infections and dental queries (Shimauchi *et al*., 2008; Masdea *et al*., 2012). Various microbes play an advantageous role in prevention of dental caries. It was seen in research that *L. rhamnosus* is useful in inhibiting the cariogenic activity of streptococcus, preventing the children from dental caries (Ahola *et al*., 2002) it was revealed in research that the consumption of *L. Lactobacillus rhamnosus* (LGG) in dairy products five times a week helps in decreasing *S. mutan* and thus beneficial in improving dental caries. So according to this study it was concluded that milk containing LGG is useful for treating dental caries in children (Nase *et al*., 2001). It was revealed in another research that yogurt containing *L. reuteri* when supplemented for 2 weeks helps in

reducing *S. mutanin* saliva to 80%.

Probiotics in Treatment of Bacterial Vaginosis

Supplementation of *Lactobacillus* fermentum RC14 and *L. acidophilus* or *L. rhamnosus* GR1 orally for duration of 2 months treats bacterial vaginosis in females as well as it helps in reducing the risk of reoccurrence of disease in comparison with placebo (Falagas, 2007). Lactobacilli producing are bactericidal in action to *Gardnerella vaginosis*. The mechanism involved is the production of hydrogen peroxide. So, probiotics are beneficial in preventing trichomonas and bacterial vaginosis (Maggi *et al*., 2000). Lactobacilli also produces Lactic acid which decreases vaginal pH and decreases the chances of developing bacterial vaginosis.

Potential Risks of using Probiotics

The consumption of probiotics is generally known to be safe, and precautions should be done in order to utilize it safely in patients that are hospitalized and are critically ill, have weak immune system or are immuno-compromised; and who are patients of AIDS. There are chances of complications if not consumed appropriately. Some of them are written below but still more research is needed in this field.

Infectious endocarditis

Generally, the status of lactobacilli is considered as "safe" but it was reported by Maskell and Pead (1992) that lactobacilli is an emerging pathogen when they are separated from the blood culture because they are being used as broad-spectrum antibiotics, reduced immunity and the increase in the life expectancy because of using upto-date medical practices and increasing the life expectancy (Maskell and Pead, 1992; Chomarat and Espinouse, 1992).

Infectious endocarditis may also be caused by probiotic microorganisms because they can aggregate platelets and then they colonize endothelial cells with bacteria due to platelet-fibrin clot. According to a study it was reported that platelets have potential to aggregate oral lactobacilli and can lead to infectious endocarditis. Selection should be done appropriately when strains are being selected for using as probiotics (Harty *et al*., 1994; Salvana and Frank, 2006).

Bacteremia

Husni *et al*. (1997) reported that forty-five patients in USA got bacteremia because of lactobacilli separated after culture in 5 years. Out of those 45 patients, twenty-seven patients have polymicrobial bacteremia. But it is not explained that either these patients had some other diseases like diabetes mellitus, cancer or those patients were immuno-compromised. Information available about supplementing probiotics with diet is not adequate.

A report showed the patient of septic pulmonary emboli and bacteremia suspected with Hodgkin's and AIDS. The patient has already been supplemented with *Lactobacillus acidophilus* probiotic but by using molecular method it was known that separated form of that strain did not resemble with probiotic strain so it was predicted that this strain might be originated from gut flora of patient (Ledoux *et al*., 2006). It was reported by Kunz *et al*. (2004) that two patients after getting probiotic therapy also developed lactobacillus bacteremia.

Pneumonia

One case of pneumonia was reported when who was 11 months of age and have trisomy 21 and were diagnosed with respiratory syncytial virus. When patients were supplemented with *Lactobacillus rhamnosus,* they developed superadded bacterial infection. Some patients that have AIDS, found to have lactobacillus pneumonia when having lung transplantation and liver transplantation (Abgrall *et al*., 1997; Jones *et al*., 1994; Patel *et al*., 1994).

Liver abcess

A lot of data is present that shows the role of probiotics leading to the liver abcess. A single case of male patient was reported who was 27-year-old and was diagnosed to have stenosis with terminal ileum with liver abscess and used steroids as a treatment. *L. acidophilus* was separated from pus culture and blood when abscess was drained (Cukovic-Cavka *et al*., 2006).

Pancreatitis

A total of 298 patients were treated with double blind, placebo controlled, randomized and it was predicted to have acute pancreatitis in severe stage. When the patients were supplemented with multispecies probiotics, mortality rate increases (Besselink *et al*., 2008).

Septicemia

The reported cases of *Saccharomyces cerevisiae fungemia* are 50, among these 50 patient's halves of patients are using probiotic products containing *S. boulardii* (Lherm *et al*., 2002; Munoz *et al*., 2005).

Transfer of antibiotic resistance

Different strains of probiotics like *Bifidobacterium* or *Lactobacillus* may or may not possess resistance for antimicrobials. *Lactobacillus* strains are resistant to vancomycin that is an antibiotic, but some strains of *Bifidobacterium* are resistant and not all to vancomycin.

Some studies reveal that the bacterial (i.e., *Enterococci*) gene vanA can be transferred to a strain of probiotics like *L. acidophilus* that is used in various products (Mater *et al*., 2005; Mater *et al*., 2008).

The bacterium that is transformed has the ability to persist in digestive tract. Hence the presence of genes having antibiotic resistance is of serious concern in patients in hospitals. Some isolated species of *Lactobacilli* and *Bifidobacteria* are found to have resistance to erythromycin and tetracycline (Ammor *et al*., 2007).

Some antibiotic resistance genes can be found on chromosomes of *Bifidobacterium* or *Lactobacillus* strains but recently it was found that they can also be present on plasmids. (Florez *et al*., 2006) and mobile DNA-elements (Ammor *et al*., 2007; Alvarez-Martin *et al*., 2007; Florez *et al*., 2008; Ammor *et al*., 2008). Antibiotic resistance genes can be transferred to pathogenic bacteria if they are present on elements of mobile DNA or plasmids. Precautions should be taken when consuming probiotics in order to avoid antibiotic resistant genes.

CONCLUSION

Based on the above discussion, it is concluded that Probiotics are used to overcome malnutrition, restore intestinal microflora and provide many benefits to consumers. These are an important component of fermented foods and food products, and different countries implement policies for the use of them in maintaining healthy lifestyle. These include a large diversity of bacterial species like *Lactobacillus* species, *Bifidobacterium* species, lactic acid and non-lactic acid bacterial species, etc. They prevent entry of pathogens into the body, change intestinal permeability and some produce antimicrobial substances as well. Still there is need to explore more about the better usage of probiotics and their proper dosage. However, there is still a need to explore more about the better usage of probiotics and their proper dosage for consumers.

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