Review Article

Epistemology of Probiotics

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ABSTRACT

Probiotics are essential in human physiology. They play a vital role in providing immunity, producing Vitamin K, relieving lactose intolerance and shortening diarrhea. Besides; it promises the management of Atopy and other incurable conditions. Not only for humans but probiotics are also beneficial for other species including marine and cattle due to the Ecophysiological responses. Unfortunately, probiotics are much neglected by the wide use of antibiotics and other drugs which not only disturbs but kills them completely. As a result; an individual is more vulnerable to a wide range of critical conditions that could have been avoided otherwise. These potential benefits of probiotics require much attention of the healthy consumer while in the main market for over the counter remedies. To prove these effects in treating and preventing particular diseases and increase the acceptance of probiotics by the general population more clinical studies should be conducted in this area.

Keywords: Health Effects, Immune modulation, Innate Immunity, Micro-biome, Normal flora, Probiotics.

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INTRODUCTION:

The intestinal flora of human body is altered, modified, and reinstated with help of the Probiotics that help in maintaining the homeostasis in the intestinal environment. In past few decades, various researches have been conducted on probiotics. The common probiotic strains are Bifidobacterium, Lactobacilli, S. boulardii, B. coagulans. When these Probiotics are fed along with the Prebiotic, for example, fructooligosaccharide (FOS), Galacto-oligosaccharides (GOS), Xylooligosaccharides (XOS), Inulin; fructans, are termed as synbiotics, which produce various physiological functions in the human body.[1]

METHODOLOGY:

The present study was reviewed from January to March 2020 by using the search engine "Pubmed and science finder". The keywords that were used to gather the information were probiotics, micro-biome, innate immunity, normal flora, health effects, and immune modulation. The large gap was present that focus on epistemology of probiotics from in previous years. Therefore, the emphasis of the review was to gather the previous researches that are especially conducted between 2015 and 2020. The highlighted points that address the detailed epistemology of probiotics in this review are etymology, intestinal microflora, contribution to resistance, causes of induced changes in intestinal flora, indications, adverse effects, and scientific guidelines for testing.

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Literature review

Etymology: According to literature review, it is said to be a full Greek etymology but it is widely considered as a combination of two Latin words of "Pro" meaning "For" and Greek adjective "biôtikos" which means "fit for life or lively". It is also considered to be derived from the word "Bios" which means "Life".[2]

Definition: Probiotics were previously defined as "A substance produced by one Protozoan which stimulated another" by Lilly and Stillwell in1965. Later various modifications were made and it was considered as 'A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance'. The revision of the definition cleared the confusion caused by the word 'substance' and emphasized 'Live cells' to be the important component of Probiotics [3]

WHO defined Probiotics in 2001 as microorganisms when administered in adequate amounts is confered a health benefit on the host. "Although this definition was widely accepted all around the world, but the European Food Safety Authority had reservations due to lack of measurability of health claims embedded by the probiotics.

The following year, in Oct 2002 they along with FAO (Food and Agriculture Organization gave the guidelines for the Evaluation of Probiotics in Food. Globally efforts were made in 2010 for the first time when academic expert scientists along with representatives from the industrial

world evaluated and recommended for the use of probiotics.

History: The first instance of use of probiotics can be traced to the Greeks and the Romans who used cheese and fermented products. Dairy food fermentations represent the first techniques for food preservation. The idea of colonizing the gut with beneficial bacteria was first given by in the early 20th century.[3] Research studies, manufacturers and consumers began giving their renewed attention to Probiotics in the 21st century.

In 1907, the first hypothesis was given by the along with a Russian scientist. They postulated that certain bacteria can play a positive role that would modify the normal flora in the intestines and replace them with useful microbes.

Metchnikoff gave the postulate which stated that the process of aging to be associated with the putrefactive or the proteolytic bacteria which produces toxic substances in the large bowl. [4] Clostridia, which resides in the intestinal lining, produces , , and with the breakdown of proteins. All these substances are toxic. He mentioned these compounds to be playing key role in "intestinal autointoxication" which with time results in the deteriorative effects of old age. The fermentation of lactose caused by the lactic acid bacteria results in lower pH by the fermented milk which resulted in inhibition of growth of proteolytic bacteria. Henry Tissier was the first to isolate from the breastfed infants. It was named Bacillus bifiduscommunis and later renamed to Bifidobacterium. He came across the use of bifidobacteria and its clinical benefits of treating infant diarrhea. Alfred Nissle in 1917 isolated a strain of E. coli from the feces of a disease-free soldier during the outbreak of Shigellosis. At that time antibiotics were not yet discovered and the management of crisis caused by Shigellosis had to be managed otherwise. He used the strains of E. coli in cases of acute infectious shigellosis and salmonellosis. Rettger and Cheplin, in 1920 conducted experimental studies in rats and human volunteers. In his study, the subjects were fed with , which showed elimination of the pathogenic bacteria like along with other gas-producing bacteria.[4]

Composition: Most of the probiotics available over the counter are composed of Lactobacilli along with Streptococci. It is also seen that Lactobacilli decreases the growth of E.Coli. Few of them also contain bifidobacteria. They may be containing a single strain of bacteria or multiple ranging from 2 to 8 strains in a single preparation. L. bulgaricus, L. acidophilus, L. casei, L. helveticus, L. lactis, L. salivarius, L. plantarum, Streptococcus thermophilus, Enterococcus faecium, Ent.faecalis, BiJidobacterium spp. and E. coli are the most common species used in currently available probiotics. These are all intestinal strains of bacteria except L. bulgaricus and Strep. thermophilus, which are used to produced yogurt. It is regarded as the safest source of probiotic available.[5]

Sources: Probiotics are commonly available as fermented dairy products, other fermented foods or probiotic fortified foods. Sources of these fermented products which contain Lactic Acid Bacteria, which is one of the important Probiotic are the pickled vegetables, kimchi, paocai and sauerkraut, Temph, miso, and soy sauce are the soy products rich in Probiotics whereas yogurt, kefir and buttermilk are the dairy ones. Sauerkraut which an Eastern and Central Asian dish in which raw cabbage is finely cut and has been fermented by lactic acid bacteria. The probiotic bacteria found in it includes , Lactobacillus plantarum, Pediococcuspentosaceus, Lactobacillus brevis, Leuconostoccitreum, Leuconostocargentinum, Lactobacillus coryniformis, and Weissella spp.[6] Kimchi, a Korean traditional dish comprising of salted and fermented vegetables including cabbage, radish, mixed with a wide variety of spices, including gochugaru, spring onions, garlic, ginger, and jeotgal. They contain the strains of Leuconostoc spp., Weissella spp., and Lactobacillus spp. Paocai is found in Sichuan cuisine, in China which comprises pickled cabbage, mustard stems, long beans, peppers, daikon, carrots and ginger. It contains L. pentosus,?L. plantarum,?Leuconostocmesenteroides, L. brevis, L. lactis, and L. fermentum. Kefir is originated from North Caucasus. It is taken from kefir grains which is a type of mesophilic symbiotic culture. It appears like fermented milk drink, like thin yogurt. They contain , , , subsp. bulgaricus, Lactobacillus helveticus, Lactobacillus kefiranofaciens, Lactococcuslactis, and Leuconostocspecies. Buttermilk is simple the fermented dairy milk. It is the liquid left after the churning of butter or cultured cream out of the milk. These days buttermilk is also cultured and it contains either or L. bulgaricus. Other sources include which comprises of along with sp., Acetobacterpasteurianus, A. aceti, and Gluconobacteroxydans.

Administration: There are various methods of administrating probiotics in human body depending upon the condition. They can be added in our daily meals or made into capsules, tablets, pastes, granules, or powder which can be taken directly.[7]

Consumption: Approximately, 41 billion USD were estimated to be the global retail market value for Probiotics in 2015. It included fermented milk products and yogurt which almost accounted for more than half of the total consumption.[8] The innovations in the probiotics mainly from supplements produced almost 4 billion USD which was projected to grow 37% globally in 2020. It was seen in China in 2014 to be rising every year by 20%.[8]

Mode of Action: There are two main mechanisms by which probiotics produce beneficial effects. Firstly, by producing a direct antagonizing effect against the pathogenic bacteria which results in decrease in their number. Secondly, by producing an immunomodulatory effect on the human body with their metabolism directly or by the stimulation of immune response of the body. These mechanisms are well supported by the experimental data.[9] Probiotics also produce

antibacterial substances that cause suppression of the pathogenic bacteria. These antibacterial substances include primary metabolites like hydrogen peroxide and organic acids. Other antibacterial substances with high molecular weight are seen to be produced by lactic acid bacteria but the inhibitory effects accounted are due to the low pH caused and the primary metabolites. Unfortunately, both of them are not active in intestine.[10] Competitive inhibition of the adhesion sites is the other mechanism that plays a vital role in eliminating the pathogenic bacteria from the epithelial lining of the intestines. Probiotics also produce useful enzymes like 8-galactosidase which is useful in conditions like lactose intolerance. The intestines of individuals with normal flora are seen to have more phagocytic activity and production of immunoglobulin when compared with a sterile gut. Ingestion of yogurt has shown increased levels of immunoglobulins when fed to germ-free mice.[11] Tumor growth is also seen to be affected by the lactobacilli showing promising results for their role in cancer prevention. Although to date there is no clinical evidence of it and further studies are required to be carried out in this regard.

Intestinal Microflora and its contribution to resistance

The micro-organisms are acquired by the human body, the moment it passes through the vagina, leaving the sterile in utero environment. This introduction of micro-organisms in the human body leads to rapid increase in their number with time and it stabilizes as a very complex collection of around 1014 micro-organisms comprising 400 different types of bacteria. [12] Various interrelationships forms between these different microorganisms and the host. They are not only subjected to the antimicrobial chemicals produced by the host cells but also the mechanical effects of peristalsis which flushes out the micro-organism along with the food. This is combated by the micro-organisms either by immobilizing and adhering themselves on the intestinal wall or by replicating at a rate more than the rate of elimination.[13]They help in preventing the invasion of pathogenic bacteria by adhering themselves to the sites and blocking the receptors. This protective effect of micro-organisms in the intestines is proven by the fact that the germ-free animals are more prone to diseases that are otherwise not seen in their corresponding conventional animals with the intestinal flora.[14]

Causes of induced changes in Intestinal Flora:

This stabilized gut flora gets disturbed due to some dietary and environmental factors which include excessive hygienic measures antibiotic therapies and stress. The most common condition arising due to lack of normal flora is diarrhea which results due to extensive antibiotic treatment. Administration of oral antibiotics also causes pseudomembranous colitis and Candida infections. Stress also triggers the disruption in the replication of gut flora. It results in decrease lactobacilli and increase in coliforms. It most commonly results from abrupt changes in the emotional or physical environment of a person. Production of cortisol along with other hormonal changes affects the mucous production which results in reduction of gut flora associated with it. Stress most commonly results from abrupt changes in the emotional or physical environment of a person. Production of cortisol along with other hormonal changes affects the mucous production which results in reduction of gut flora associated with it. Space travelers also experience changes in their flora resulting in diarrhea like conditions. All these conditions can be managed by giving the Probiotics. Hence, it has much potential value as all these conditions are seen to be resolved once the gut flora is restored.

Indications

Antibiotic-associated diarrhea

Children are most prone to infections for which wide range of antibiotics are administered to them regularly. During this frequent administration of antibiotics among children, approximately 11% to 40% develop antibiotic-associated diarrhea.[15] When there is imbalance in the intestinal normal flora resulting due to administration of antibiotics, it results in Antibiotic-associated diarrhea. This results in osmotic diarrhea caused by less absorption of short-chain fatty acid due to disturbance in the carbohydrate metabolism. According to, a review conducted in the year 2015, some protective effects were observed in children having antibiotic-associated diarrhea with the use of probiotics. It also showed reducing the occurrence of Clostridium difficiledisease. Several meta-analyses showed positive results for probiotic treatment to be effective in reducing the occurrence, severity and disease progression in Antibiotic-associated diarrhea. Along with reduction in Antibiotic-associated diarrhea, improved stool consistency while on antibiotics and better immune response after vaccinations are with probiotic formulations containing L. rhamnosus was also observed.[16] Probiotic strains used and their dosage is responsible for the efficacy of the probiotic preparations in treating Antibiotic-associated diarrhea. A study showed use of 5 to 40 billion colony forming units/day of L. rhamnosus or in children for the management of Antibiotic-associated diarrhea. This shows that the adverse effects associated with the probiotics can be rare whereas same study states its adverse effects being much when used in debilitated or immune-compromised children.[17]

Immune modulation: Probiotics prevent invasion of pathogenic bacteria with help of competitive inhibition. They also aid the production of IgA by the plasma cells and enhances the process of phagocytosis. It also causes an increase in the proportion of T lymphocytes and the natural killer cells.[18]

Bacterial vaginosis: In case of bacterial vaginosis, probiotic treatment is the application or ingestion of bacteria that are otherwise found in healthy vagina. This helps in curing the infection at a much faster rate.[19] The vaginal flora in healthy

females is 70% Lactobacillus which inhibits the invasion of pathogenic bacteria.

Hypertension: Very limited data is present giving evidence of direct link between hypertension and the use of probiotics. Further studies are required to be carried out to support the data.[20]

Dermatitis: Data supporting the effect of probiotics in conditions like dermatitis is also inconsistent and the American Academy of Dermatology state that the use of probiotics due to lack of evidence to be not recommended in patients of Atopic dermatitis.[21]

Helicobacter pylori: Peptic ulcer caused by Helicobacter pylori is seen to be prevented with the use of lactic acid bacteria in combination with medical treatment. Further studies are required in this regard for the establishment of standard in medical practice.[22]

Intestinal infections: Normal flora present in the gut is observed to be active against E. coli, Campylobacter fetus subsp. jejuni, Clostridium perfringens, Cl. botulinurn, and Yersinia enterocolitica.[23] The particular bacteria which causes this decrease in the pathogenic bacterial growth are yet to be identified.[24]

Lactose intolerance: Lactose intolerance is found commonly all around the world. It results from deficiency of an enzyme p-galactosidase which causes inability to breakdown lactose. Such people are seen to be able to digest lactose when given yogurt as compared to in milk which is confirmed by the Hydrogen breath analysis.[25]

Constipation: Lactobacili also plays an important role in relieving constipation. Acidophilus milk has given significant results as a treatment option for constipation as seen in patients fed with supplements of L.acidophilus having better bowel functions.[26]

Tumors: Lactobacilli produces antitumor or anti-carcinogenic effects by inhibiting the tumor cells directly or by suppressing the growth of bacteria causing production of enzymes responsible for the production of carcinogens from innocuous compounds. These enzymes include p-glucosidase, 8-glucuronidase and azoreductase.[27] They are also found to be responsible for the destruction of nitrosamines which are potent carcinogens and suppression of its precursor nitroreductase.

Hypercholesteremia: Intake of yogurt was seen to have lowering effects on blood cholesterol. These effects were due to the presence of bacterial metabolites resulting in inhibition of cholesterol synthesis in the human body. Some lactobacilli are seen to have direct effect on cholesterol levels by assimilation and elimination from the growth medium.[28] A study conducted in 2002, concluded through a meta-analysis of five double-blinded clinical trials, states that it was observed that the use of yogurt having probiotic strains had an effect on total cholesterol levels with a decrease of 8.5Êmg/dl (0.22Êmmol/l) (4% decrease) and an decrease in serum LDL concentration of 7.7Êmg/dl (0.2Êmmol/l) (5% decrease).[29]

Allergies: People having milk allergy are indicated to have probiotics. Although there is no much data to support the statement. It was seen in a study conducted in 2015 that probiotics when given to infants with eczema, or the infants whose mother underwent probiotic therapy during their pregnancy and breastfeeding stage had less likelihood of developing eczema.[30]

Respiratory Tract Infection: A decrease in the incidence of RTIs was observed in reviews reported in adults.[31]

Inflammatory bowel disease

Standard medication along with the administration of probiotics is seen to be effective in the management of ulcerative colitis but no role was observed in cases of Crohn's disease.[32]

Recurrent abdominal pain: According to a study conducted in 2017, it was suggested that the use of probiotics helps in relieving abdominal pain in short term in children. Proper strains and dosage causing these effects are yet to be worked on.[33]

Asthma: Quality of research is low in this area as well, but literature review does give us some studies showing evidence of probiotic supplementation to be helpful with childhood asthma[34]

Dental Caries: Decrease in the dental caries index was seen as a result of a large study conducted on children.

Adverse effects: On some occasions, bacterial-host interactions are observed after administration of Probiotics. Regardless of this fact, generally probiotics are considered safe, except for few concerns. The conditions which make certain people more likely of having adverse effects include, immunodeficiency, short bowel syndrome, central venous catheters, cardiac valve disease, and premature infants.[35] There exist an evident risk in cases of severe inflammatory bowel disease, which may allow the passage of viable bacteria from the intestinal lining to the internal organs with the blood vessels, and give rise to bacteremia which may further cause adverse consequences.[36] This may also be observed in certain cases of children with low immunity. It can lead to sepsis and can prove fatal. Obesity is also liked with Lactobacillus spp. but it does not have enough evidence to establish any certain relationship.

Scientific guidelines for testing: During administration, the probiotics should be alive. The viability and reproducibility at the time of administration are the main concerns according to the literature review, along with the viability and stability during the shelf life and after once being administered in the stomach and intestinal environments.[37]At the genus, specie and strain levels, they should be taxonomically defined microbes or combinations

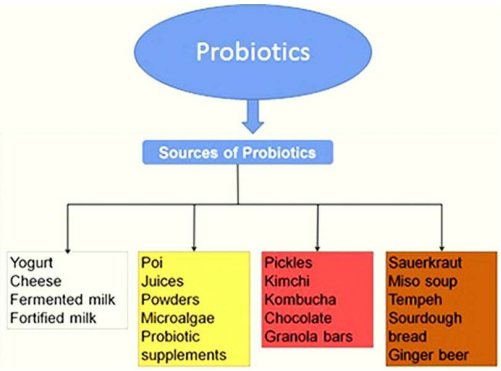
of microbes which requires very precise strain identification.[38] They should be biocompatible and safe for administration.[39]

FAO and WHO have given guidelines[40] which recommends that bacterial strains which may generally be recognized as safe (GRAS) should be evaluated for their safety as a potential probiotic with help of minimum required test:

- Should belong to a strain of bacteria capable of producing beneficial effects in the human body.
- Should be safe, non-toxic, and non-pathogenic.
- Should not have any adverse effects.
- Should be found as viable cells, so effective dosage can be given.
- Should be able to survive, metabolize and reproduce in the gut environment.
- Should be able to be stored for long periods under storage and field conditions.
- Antibiotic resistance patterns should be determined.
- Should be assessed of metabolic activities.
- Epidemiological surveillance of adverse incidents should be carried out in consumers.

Scope of Research: Regardless of the beneficial effects, the clinical use of probiotics is its early stages. Further studies and clinical trials are much required to establish evidence. Although being popular in most parts of the world, the scientific data does not exactly prove any cause and effect relationship. They are still subject to preliminary research for the evaluation of their physiological effects in the human body according to the European Food Safety Authority. It is believed that the beneficial effects of Probiotics are due to long-term healthy dietary changes. Although it remains controversial it is also proposed by the use of probiotics mainly the lactobacilli to be playing role in obesity. A controlled evaluation should be carried out for the documentation of its health benefits. Products which comprises of live organisms that may reproduce in the intestines should be considered only.

Figure 1: Foods rich with probiotics



CONCLUSION:

Probiotics are non-pathogenic micro-organisms which are administered to improve the microbial balance in the human body. They produce their physiological effects through various mechanisms, which may include, change in pH-causing more acidity, decreasing invasion of pathogenic bacteria by competitive inhibition and immune modulation. Dosage and the type of bacterial strain to be used need to be established by conducting clinical trials.

Author Contribution:
Aafaq Khan: Conceptualization and Reviewing
Naveed Faraz: Literature survey
Faisal Hanif: Writing-original draft preparation
Mahparah Mumtaz: Editing and reviewing

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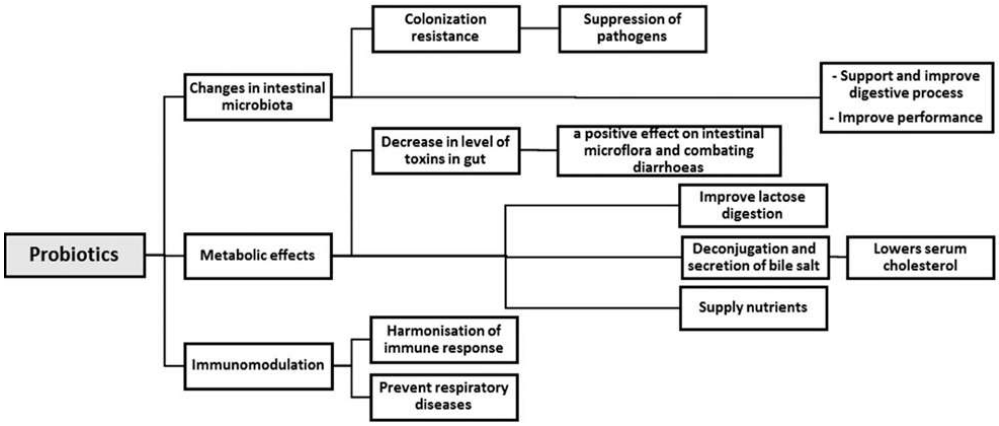
Figure 2: Metabolic effects of Probiotics



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