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Probiotics Mitigate the Anti-Cancer Effect of Drugs: A Review

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Abstract

This study was conducted at Department of Zoology, University of Gujrat, Pakistan during 2016-2017. The data regarding causes, effects and treatment of various types of probiotics was obtained and compiled through a thorough review of various published research articles of international reputed journals and relevant books. As energy food probiotics have proven their efficacy in preventing several types of cancer. Probiotics effect by competing for nutrients and receptors by producing antimicrobial metabolites. Metabolites produced by probiotics are for protection against cancer, and using mutagens, diminishing marginal productivity of 30 carcinogens by mitigating xenobiotic metabolism hormone regulating apoptosis and suppressing multiplication. In addition, probiotics alter the physiology and mental health counseling the reduced risk of carcinogenesis. Therefore, probiotics would be considered safe strategy to prevent cancer.

Keywords: Probiotics, Prebiotics, Synbiotics, Carcinogenesis, Apoptosis

INTRODUCTION

The word cancer is frightening the world. The cancer patients seem to be stranded because the rate of survival is very low, if survive, recovery is very challenging. Cancer is a generic term for a large group of diseases that can affect any part of our body. It is one of the major leading causes of death worldwide and obviously has gained much attention of scientific community to develop and improve the cancer treatment with the intention to reduce the side effects of existing treatments and also makes expensive drugs affordable to common man [1, 2]. The primary goal of scientific community involved in cancer research is to kill the disease or if not at least continue efforts need to be made considerably to prolong the life of patients by improving the quality of life. Although many drugs are used to treat cancer, tolerance to their burden is really a challenging task. As it is good that the prevention is better than cure

so an alternative to drugs in preventing cancer is the use of natural foods that confer the anti-carcinogenic effects.

In recent years the intervention to prevent cancer has received an incredible attention from clinical nutritionist, scientists and industrialists. The World Health Organization defined probiotics as live microorganisms which when administrated in adequate amounts confer a health benefit on the host [3].

Marcel Roberfroidwho identified and named prebiotics first in 1995 defined that prebiotic is a selectively fermented ingredient that allows specific changes both in the composition and activity in the gastrointestinal micro-flora that controls benefits upon host well-being and health [4]. Probiotics provide health benefits by enhancing digestion and absorption of nutrients, modulating immune responses, balancing the population of beneficial bacteria, excluding pathogens and producing essential vitamins and amino acids [5].The mechanism of probiotic action primarily includes alteration in the composition of gut micro-biota, maintaining epithelial barriers function, competition with nutrients and adhesion to the epithelium of the gastrointestinal tract. Probiotics enhance the host immunity to pathogens by producing antibacterial substances that result in the suppression of specific pathogens [6, 7]. There are certain species of intestinal micro-biota particularly lactic acid bacteria which exhibits anti-carcinogenic action, anti-inflammatory effects also takes part in alleviating the symptoms of lactose intolerance [8, 9]. Lactic acid bacteria also exhibit anti-cholesterol activities and decrease cholesterol levels by producing lipase and by assimilating fat in the body [10].

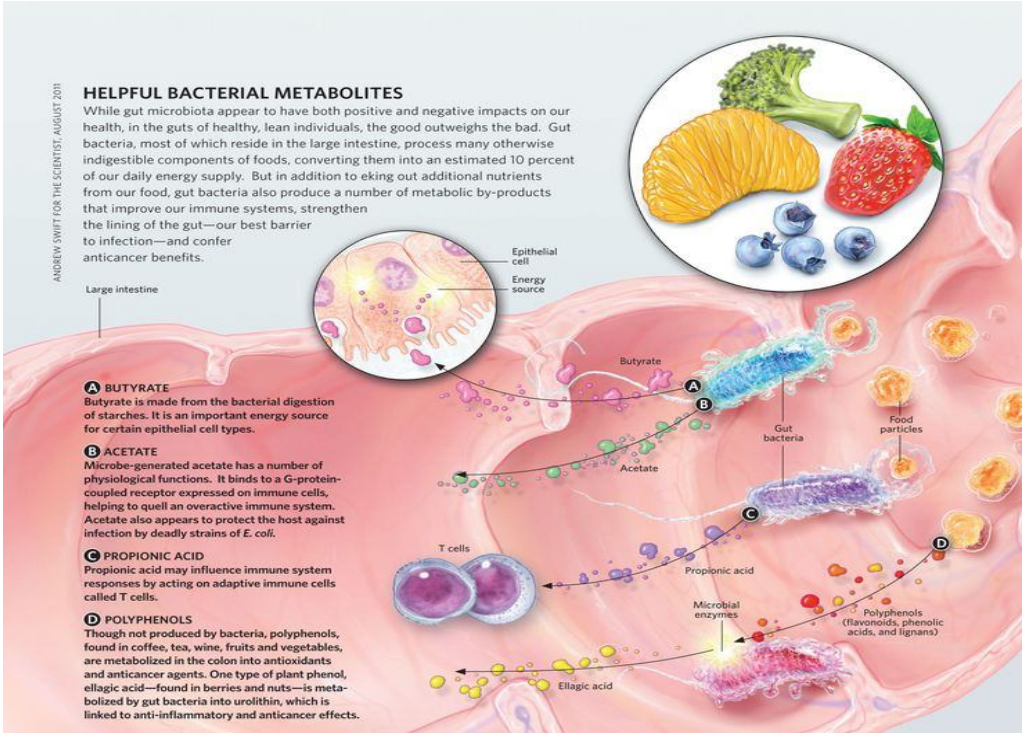

Figure 1: The helpful bacterial metabolites are shown. These include Butyrate, Acetate, Propionic acid and Polyphenols. These bacterial metabolites improve immune system, strengthen the lining of gut, act as best barrier to infection and confer anti-cancer benefits.

DIFFERENT STRATEGIES BY WHICH PROBIOTICS CONFER PROTECTION AGAINST CARCINOGENESIS

Exclusion of Pathogenic Microorganisms

Severe microbial infections are known to associate with the development of cancer and it has been reported that 17.8% of the global cancer burden is due to infection. However in the developing countries the rate of infection associated with cancer is 26.3% while in the developed countries the rate has been reduced to 7.7% [11]. 15.6% of the worldwide cancer was caused by the infection with bacterium Helicobacter pylori and viruses such as hepatitis B, hepatitis C, human papillomavirus, human lympho-tropic virus 1 (HLTV1), Epstein Barr virus and HIV virus [12, 13]. Epstein Barr virus has proven to cause Burkitt's lymphoma, nasopharyngeal carcinoma and many other types of lymphomas [14]while HTLV1 causes adult T-cell leukemia [15]. Whereas human papilloma virus causes bladder carcinoma [16] and parasites like liver fluke causes cancer of liver [17]. Probiotics are known to eliminate pathogens in the gut by inhibiting and displacing their adhesion by competing for the receptors on epithelial cells nutrients producing antimicrobial metabolites and strengthening the intestinal barrier. Probiotics inhibit the expression of genes for virulence and proteins by interpreting the signal transduction pathway of pathogens [18, 19]. So prebiotics serve as an effective tool in eliminating pathogens and protecting the host from pathogenic carcinogenesis.

Anti-Mutagenic Property of Probiotics

Development of cancer is a multi-stage process that would initiate when mutations start to accumulate in the tumor suppressor and promoted oncogenes [20]. The intestinal microorganisms produce geno-toxic compounds that contribute to the increased risk of carcinogenesis. Some of the beneficial intestinal bacteria mitigate the formation of mutagens and their effects. Balanced diet helps in the establishment of good micro-biota which is beneficial to the host while imbalanced food that is high protein and fat content with low fibermay increase the occurrence of harmful microorganisms in the intestine [21].

Xenobiotic Enzymes

Xenobiotic enzymes also take part in the development of carcinogenesis. The enzymes responsible for the xenobiotic metabolism are generally referred as xenobiotic metabolic enzymes or xenobiotic enzyme.Xenobiotic metabolizing enzymes increase the geno-toxicity and carcinogenicity in the colon [22]. There are various species of probiotics which inhibit or mitigate activity on xenobiotic enzymes. For example, probiotic bacteria such as Lactobacillus acidophilus hindered the conversion of exogenously administered aromatic nitro-azo and amine glucuronide compounds to free amines [23]. So bacterial xenobiotic enzyme activity is strain specific and probiotic strains which are proven effective can be used to prevent xenobiotic metabolism induced carcinogenesis.

Production of Protective Metabolites

Probiotics produce a wide range of metabolites that confer health benefits to the host. The metabolites of probiotic bacteria such asarginine, glutamine, Short Chain Fatty Acids (SCFAs), bacteriocins and hydrogen peroxide are protective to the intestine [24]. Fermented metabolites are capable of inducing apoptosis, a mechanism of programmed cell death which is considered to be a promising strategy in controlling tumor genesis [25]. Butyrate nourishes the colonic mucosa and meantime it has also been proven to promote the apoptosis of transformed colonocytes. In addition, it has also been reported to inhibit histone deacetylase enzyme which together with histone acetyltransferases determine the acetylation status of histones and also affect the regulation of gene expression [26, 27]. By altering the transcription of small number of genes responsible for cell differentiation, arrest of cell growth and apoptosis in tumor cells, butyrate has proven its efficiency in the prevention and management of cancer.

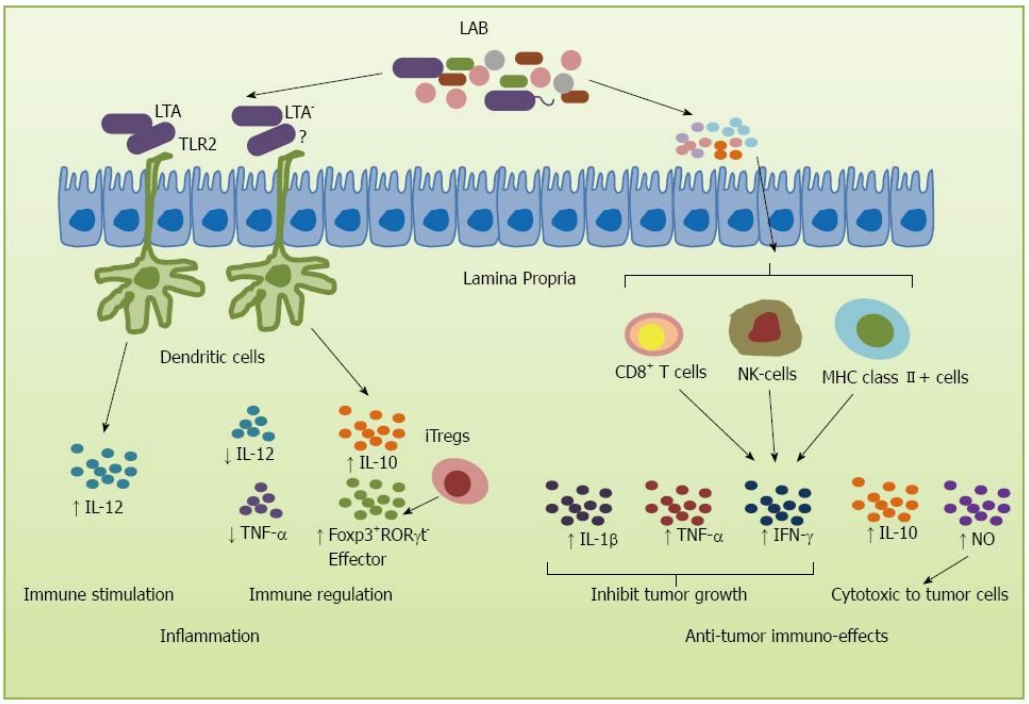

Figure 2: This figure shows the production of protective metabolites from Lactic Acid Bacteria (LAB). These metabolites trigger immune response and also exhibit anti-tumor immune-effects.

Anti-Proliferative Activity and Regulation of Apoptosis

Apoptosis is a process of programmed cell death that occurs in physiological and pathological conditions. It depletes the cancer cells and constitutes a target for anti-cancer chemotherapy. Both morphological as well as physiological changes can be observed during apoptosis. Morphological changes in nucleus mainly involve the chromatin condensation, nuclear fragmentation while cytoplasmic changes involves rounding up of the cell, pyknosis and retraction of pseudopods. The physiological changes involve activation of caspases, breakdown of DNA, and proteins, changes in the membrane and recognition of phagocytic cells [28, 29]. L. ruteri regulates cell proliferation by facilitating apoptosis of activated immune cells via inhibition of IkappaBalphaubiquitination and enhancing pro apoptotic MAPK signaling [30]. It has also been reported that probiotic isolates, L. rhamnosusandBifidobacteriumlactis induce apoptosis through mitochondrial pathway in Caco-2 cells [31]. In addition, cell bound exo-polysachcharide (cb-EPS) has also been shown to inhibit colon cancer cell line by directly affecting cell morphology [32]. The soluble polysaccharide from L. acidophilus also shows anti-cancer activity by inducing apoptosis in the HT cell line [33].

Probiotics for Altered Food Preference and Mental Health

Both human and micro-biota in the gut are mutually regulated by each other. This can be related and described as follows: the human behavior, mainly the food habit i.e. the kind of food ingested, frequency and quantity greatly determines the gut microbial composition and diversity of an individual. On the other hand, it has been well studied that gut micro-biota influence the host physiology to a greater extent, therefore, the kind of microbial diversity in the gut determines the health of an individual [34]. The fat and protein rich diet is mainly associated with the increased risk of carcinogenesis; to overcome this one has to adapt to change the food habit, preferring a balanced diet not containing high fat and protein which upon overcooking release dietary amines and other genotoxins. Further, the infusion of intestinal long chain fatty acids such as linolenic and linoleic acids modulated food preference

as well as total calorie intake via the vagal nerve and midbrain hypothalamic neural pathways [35]. In addition, the pharma-biotics such as gamma amino butyric acid (GABA), acetylcholine, serotonin, catechol-amines etc., produced by probiotics and other commensal gut micro-biota modulate neural signaling with enteric nervous system when they release into intestinal lumen [36, 37].

NEW FRONTIERS IN PROBIOTIC RESEARCH

Defined as 'live microbial feed supplements which beneficially affect the host by improving the intestinal microbial balance' [38]; probiotic bacteria represent aneffective alternative to traditional prophylactic andtherapeutic regimes in a variety of clinical settings. Certain probiotics for example have been shown to be effective in the treatment [39] andprevention [40] of rotavirus-associateddiarrhea, and also significantly reduce the incidence of antibiotic-associated diarrhea when co-administered with antibiotics [41]. Probioticshas also been implicated in the prevention and decreased recurrence of certain cancers, reducing the risk of colon cancer by inhibiting certain carcinogens, such as nitrosamines or producing anti-mutagenic com-pounds. The robotic strain Lactobacillus salivariusUCC118 e.g. has been shown to reduce the prevalence of colon cancer in interleukin-10 (IL-10) knockout mice [42].
Breast-fed infants exhibit higher bifido-bacteriacounts, which are associated with lower incidence of allergies compared with formula-fed infants [43]. In addition, Lactobacillus GG has been shown tosignificantly reduce the incidence of eczema in the first 2years of life in high-risk infants, when administered tothe mother for 2 weeks prenatally and to the infants for 6months post-natally. The frequency of eczema in the pro-biotic-fed group was half that of the placebo-control group [44].

Improving Probiotic Delivery – Patho-Biotechnology

Current methods to improve probiotic survival involve the induction of a stress-tolerance response achieved bypre-exposing cells to sub-lethal stresses, such as salt, heat, bile and low pH [44]. Such pre-exposure can significantly increaseprobiotic survival following subsequent exposure tolethal stress. Schmidt and Zink showed that pre-exposing Bifido-bacterium adolescentis to 47C for 15 minprior to a lethal heat shock increased the strain's heattolerance 128-fold [45]. Such treatments however might alsoresult in significant decreases in cell yield, in addition tocellular activity and process volumetric productivity [46]. An alternative approach to improving probiotic efficacy is to enhance a strain's ability to cope with stress at the genetic level.

Improving Probiotic Specificity – 'Designer Probiotics'

The most significant applications of designer probiotics to date include the treatment of HIV (AIDS) and enteric infections.

HIV (AIDS)

Approximately 14 000 people contract HIV every day[47].One such strategy, presented by Rao, involves the use of a live microbe-cide [48]. They constructed a genetically engineered probiotic E. coli strain that secretes an anti-HIV peptide derived from the C-terminal heptad repeat (HR-2) region of the trans-membrane subunit of the HIV-1 envelope glycoprotein (Env), and functions by blocking HIV entry to the host cells. When administered orally or as a rectal suppository, this 'live microbe-cide' colonizes the gut mucosa and secretes thepeptide in situ, thereby providing protection in advance ofHIV exposure for up to a month (Laurel and Berger 2005).Using a similar approach, Chang engineeredthe commensal bacterium L. casei to secrete two-domainCD4 proteins [49]. In this approach, the proteins bind HIVtype-1 gp20 and inhibit entry into host target cells.

Enteric Infections

Many of the pathogens responsible for the major enteric infections exploit oligosaccharides on the surface of host cells as receptors for toxins and / or adhesins, enabling colonization of the mucosa and entry of the pathogen orsecreted toxins into the host cell. Blocking this

adherenceprevents infection, while toxin neutralization ameliorates (improves) the symptoms until the pathogen is eventually overcome bythe immune system. When administered orally, these probiotics bind to and neutralize toxins in the gut lumenand interfere with pathogen adherence to the. One such construct consists of an E. colistrain expressing a chimeric lipopolysaccharide (LPS) terminating in a shiga toxin (Stx) receptor. One milligramdry weight of this recombinant strain has been shown to neutralize>100 lg of Stx1 and Stx2 [51]. Paton have also constructed probioticswith receptor-blocking potential against Entero-toxigenicE. coli (ETEC) toxin LT and cholera toxin (Ctx) [52, 53].

FUNCTION OF PROBIOTICS AS EFFECTIVE PROPHYLACTIC AGENTS

In addition to a therapeutic role, certain probioticshave also been shown to function as effective prophylacticagents, being specifically engineered to function as novel vaccine delivery vehicles. Stimulating both innate and acquired immunity, these strains lack the possibility of reversion to virulence, which exists with the more conventional pathogenic platforms currently in development.Guimara˜esrecently described the construction of a L. lactis strain expressing inlA, encoding inter-nalin A, a surface protein related to invasion inL. Mono-cytogenes [54]. In this instance, the otherwise non-invasive L. lactis strain is now capable of invading the smallintestine and delivering molecules (DNA or protein) into-mammalian epithelial cells, making it a safer and moreattractive alternative to attenuated L. mono-cytogenes as anantigen-delivery vehicle. Probiotic vaccine carriers administered by the mucosal route mimic the immune responseelicited by natural infection and can lead to long-lastingprotective mucosal and systemic responses [55]. Mucosal vaccine delivery (thoseadministered orally, anally or by nasal spray) also offerssignificant technological and commercial advantages overtraditional formulations, including reduced pain and thepossibility of cross-contamination associated with intra-muscular injection and the lack of a requirement formedically trained personnel to administer the vaccine.

CONCLUSION

Probiotics and prebiotics selectively modulate the gut micro-biota, eliminating pathogens, reducing mutagenicity and geno-toxicity of dietary carcinogens, suppressing xenobiotic enzyme activity, preventing the release and reabsorption of pro-carcinogenic substances, producing metabolites with anticancer properties, regulating apoptosis, and modulating immunity, confer protection against carcinogenesis to the host. In addition, a healthy balanced diet can aid in reducing the risk of carcinogenesis. Accordingly, probiotics have also proven to alter the food preference and help an individual to adopt healthy food, thereby conferring protection. With the potential to alleviate the symptoms of chronic gastrointestinal disorders to fightinfection and modulate the immune system probiotics are finally beginning to representa viable alternative to traditional drug-based therapies [56].

FUTURE PROSPECTS

Recent developments in synthetic and systems biology, based on the rapidly advancing 'omics' technologies, has and will continue to lead to the emergenceof an ever-increasing number of novel genetic loci withdefined additional functions. This coupled with computer-aided bioinformatics and novel tools for genetic modification will ultimately lead to the development of artificialmicro-organisms [57] and eventually to a new class of probiotics assembled fromthe components of various origins and tailored to fulfil allthe requirements of an ideal therapeutic agent.

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