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"PROBIOTICS: A GIFTING TOOL FOR PREVENTION AND TREATMENT OF COLON RECTAL CANCER"

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Abstract: Colorectal cancer (CRC) is the second most deadly form of cancer with high clinical significance. The standard protocol of cancer therapy is either radiotherapy or chemotherapy but it is still doubtful and also affects the normal cell of the body. The colorectal cancer may cause by smoking or diet rich in red, processed meat and poor vegetables and fruit, and genetic predisposition. In our body there is lots of microbes at different area and they can be a beneficial. Probiotics are the "live microorganisms which are beneficial when consumed in adequate amount". Probiotics helps to prevent the cancerous effect in colon rectal. This review is focuses on the role of Probiotics as alternative tool to prevent and treat the colorectal cancer. Probiotics potential mechanisms of actions like, modification of microbiota of intestine, anti-inflammatory response, producing antioxidant metabolites, decrease the production of harmful enzymes. Probiotics are also administrating as a "BIODRUG" via any vector. The potential dose of probiotic gives their response to cancer cell. In the future, the Probiotics become a part of lifestyle and also used in prevention and treatment of cancer.

Introduction:

Colorectal cancer is the second most deadly form of the cancer (1). Many of the death is carried out because of the CRC from the past many centuries. The number of death in 2020, because of the colorectal cancer is 606,520 (2). Many researchers are trying to find the best way to prevent the cancer and that innovative way which directly or indirectly not harm the normal cell because the radiotherapy or the chemotherapy are ultimately harm the normal cells too. The risk factors for colorectal cancers are depend on genetic disturbance, red diet, non cooked meat, less consumption of vegetables and fruits. In gastrointestinal track more than million of the microorganisms are present. Some microorganisms lie *Fusobacterium* and *Porphyromonas* are identified as cancerogenic bacteria. Probiotic bacteria help to treat and prevent the cancer.

Probiotic means "live microorganisms which are beneficial when consumed in the adequate amount (3). Probiotic bacteria are mainly present in the intestine for example; *Lactobacillus, Bifidobacterium, Enterococcus, Lactococcus, Streptococcus, Vegococcus* which are gram positive and some gram negative bacteria are *Escherichia coli* and *Bacillus* (4). That is not mandatory that all the same species microorganisms have same effect on the organisms. It depends on the strain of the microorganisms but that is also true that all the strains are also not play a role as a Probiotics (5). Intestinal dysbiosis may cause

because of the tumor generation in gastrointestinal areas and tumor localized in distal sites of the body. The use of probiotics are also give a positive effect on the gut microbiome. It carries the balance of the normal microbiota in the GI track and also regulates the mechanisms and functions.

Primary prevention: Decrease the risk of external factor.

Secondary prevention: Detection of abnormality/cancer, it also includes a diet and physical actvities.

Late prevention: Reduce the risk of death.

Figure 2: The Types of Cancer Prevention (6) (7).

Probiotics:

Probiotics are a microbes which are not pathogenic, and play a vital role into the health benefits when administrate in sufficient quantities (8). The characteristics of Probiotics are resistance to acid, epithelial cell adhesion, bile tolerance, bile salt hydrolase potential, antimicrobial resistance, immunostimulation, antagonistic activities and anticarcinogenic activities (8).Probiotics and their bioactive molecules form several beneficial effect in GI tract, and release different enzymes and potential synergistic effect on digestion. Lactic acid bacteria which are the most probiotic induce the potential adjuvant effect such as cell mediated immune response modulation, reticulo-endothelial system activation, cytokine pathways augmentation, and interleukins and TNF regulation (9).

Major Probiotics carried out the anticancerous and antimutagenic activities are: Binding, degradation and inhibition of mutagens, prevent the precarcinogens and conversion of toxic, harmful and highly reactive carcinogens: pH lowering by SCFAs (Short chain fatty acids) formed during degradation of carbohydrates which are not easily digestible. Probiotics also modulate the innate immune system and enhancement carried out by secretion of anti-inflammatory molecules (10).

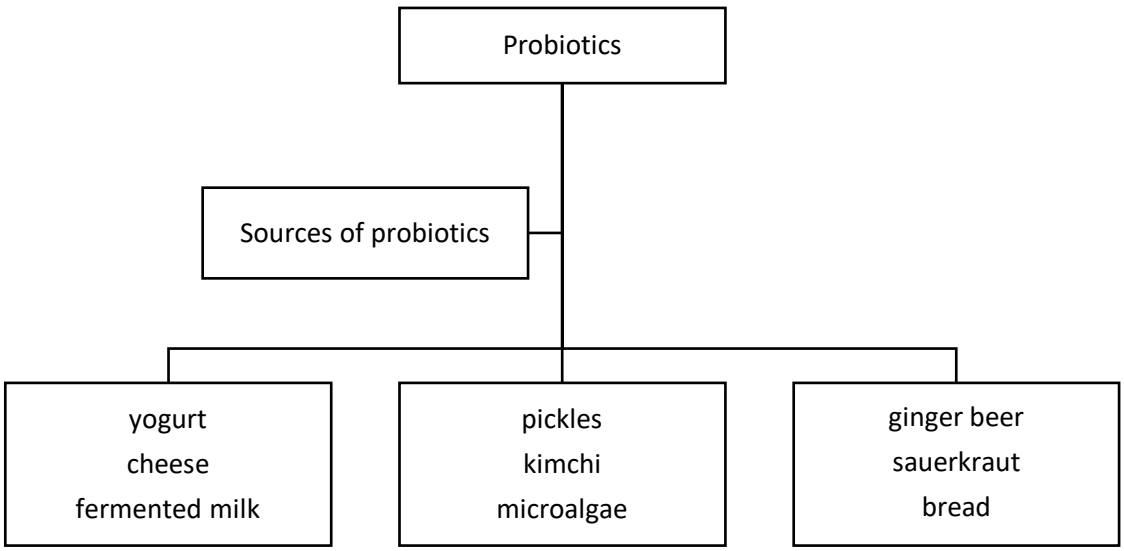

Figure 1 : Different Sources of Probiotics.

- Some examples of Probiotics microorganisms/strain effect on cancer.
    1. *Lactobacillus casei*: it having the inhibitory effect against the CRC induce the phagocytosis and also maintain the intestinal microbial communities and decrease the risk of intestinal disorders. Also carried out the protection against the mutagenic foods and decrease the effect the harmful enzymes which promote the CRC (4).
    2. *Bifidobacterium breve*: it increase the acidity in gut as a effect of probiotic and because of that the many harmful/cancer causing microorganisms are inhibited ate lower Ph (11).
    3. *Saccharomyces boulardii*: it has effect to inhibit the bacterial infection and also gives the anti-inflammatory effect. Increase the Secretion of antibodies lie IgA (12).

Probiotics and Gut microbiota:

The relationship between Probiotics microbes and gut microbiota are important in modifying the composition of gut microbiota (13). In the gut all the microbiota community are heterogeneous mostly comprise bacteria but fungi, archea and viruses are also present (14). In this whole community of bacteria of gut microbiota most of the *Firmicutes* and *Bacteroidetes* are in large amount (15). The human physiology regulated by gut microbiota which regulates the health of intestine, physiology, cellular features, development immune homeostasis and metabolism (13).

Gut microbiota produce a different metabolites and byproducts, by which microbiota protects the health of human body (16). Resident microbiota which are commensal, are able to produce hormone like metabolites includes SCFAs, by the fermentation of dietary fibers in large intestine (17). Specific composition and diet determine the nature of SCFAs which produce by microbiota. This SCFAs are the transported via bloodstream, and liver used this SCFAs as a main source of energy (18).

Many microorganisms produce the SCFAs and histone deacetylases, which have the anticancerous properties in the CRC (19). CRC is direct related with the diet, lifestyle and gut microbiota composition (20). When the dietary imbalance generated is cause the CRC because of virulence factor, inflammatory pathway and microbial metabolites. In the future, Probiotics are highly use in cancer prevention and treatment, when Probiotics consume in sufficient amount it can prevent CRC by the balancing the intestinal microbiota (13).

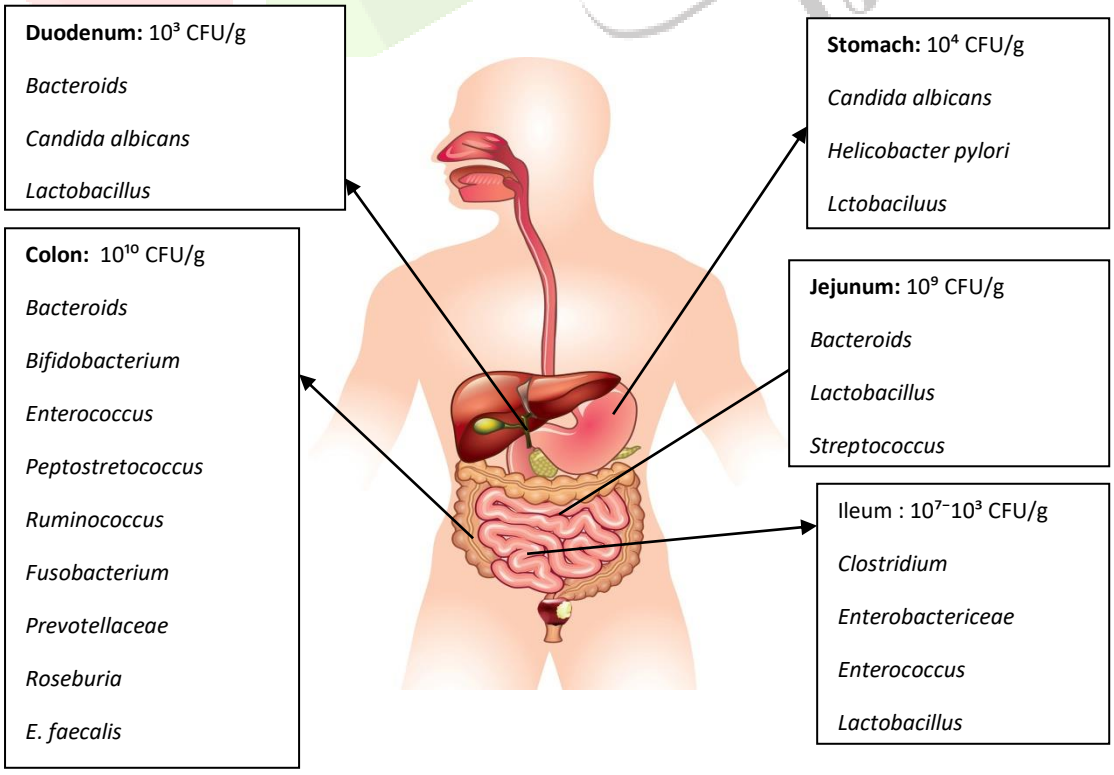

Figure 2 : Number and types of microbial population in GI tract.

Effect of Probiotics on CRC:

Probiotics	Cancer	Effect	Ref.
L. reuteri	CRC	Activate caspase activity	(21)
E. faecalis RM11	CRC	^ apoptosis	(22)
L. cocktail	CRC	Notch regulation	(23)
L. casei BL23	CRC	Caspase-7, Bik and caspase-9 regulation	(24)
E. faecalis	CRC	Inflammasome activation in macrophage by inhibit NLRP3	(25)
K. marxianus and P. kudriavzevii	CRC	^ apoptosis, and also inhibit the AKT-1,mTOR and JAK-1 pathway	(26)
L. fermentum	CRC	Propionate production	(27)

Mechanism of Probiotics on CRC:

There are many mechanisms by which the risk of colon cancer can reduce or prevent. Based on this, we can concluded that, Probiotics can reduce the risk of cancer is associated with the favorable qualitative and quantitative changes in intestinal microbiota, physiochemical activities and metabolic activities of intestine.

Action of probiotics on CRC

- Articulation in microbiota composition.
- Tight up the junction of epithelial layer.
- Increase the production on antioxidant and anticarcinogenic metabolites.
- Modulate the physiochemical condition.
- Decrease inflammation in intestine.
- Affect the harmful enzymes as well as deactivate the carcinogenic component.

➢ Articulation in microbiota composition.

In intestine, microbiota are already present and they maintain the situation and all functions of the body but When in the intestine dysbiosis situation carried out by pathogenic microbes, it makes the problems in function and composition of intestinal microbiota. And they also cause the inflammation by production of carcinogenic compounds, by which it easily converted into CRC (28).

Some research showed that, in the CRC patient *Bacteroids* and *Prevotella* are highly present. In normal intestine the *Bacteroids, Prevotella, Eubacterium, Fusobacterium* are in lower amount. sometimes in CRC patient *Salmonella* and *Clostridium* are also present in higher amount (29).

Probiotics increase the *Lactobacillus* by compete with pathogenic and putrefactive bacteria (30). *Bacteroids fragilis* is produce fragilysin enterotoxin which can cause cancer. this enterotoxin increase the proliferation of cells by actiating Wnt signaling pathway. This toxin also cause inflammation by producing inflammatory mediators and increase the risk of CRC (31).

Probiotic organisms compete with the pathogenic organisms for the space. Probiotics having antibacterial properties and ability to adhere to epithelium. Probiotic microbes produce such substances like reuterin, bacteriocins, deconjugated bile acids, lactic acids and hydrogen peroxide by this substances Probiotics inhibit the pathogenic as well as carcinogenic microorganisms (29), (4).

- **Tight up the junction of epithelial layer (epithelial barrier)**

When the mucosal integrity is disrupted, it increase the permeability of allergens and pathogens and ultimately it cause inflammation and stress condition. Pathogenic bacteria having capacity to disturb epithelial junction and cause CRC (29). Epithelial layer gives protection from toxins, pathogens as well as damage. Some junction proteins like claudin-3, occluding and junction adhesion proteins, play important role in permeability. Treatment of Lactobacillus reduce the stress and inflammation, which restore the epithelial tight junction (32).

Probiotics bacteria rebuild the epithelial barrier by prevent the rearrangement of protein entering tight junction and also increase the production of mucus by goblet cell, reduce the leakage of harmful substances which secreted by pathogens (29) (33).

- **Increase the production on antioxidant and anticarcinogenic metabolites.**

Probiotics carried out the production of SCFAs and phenols which play a role as a anti-carcinogenic compound and gives potential activity against CRC (34). SCFAs are the end product of bacterial fermentation, it SCFAs production depends on the diet, gut microbiota and metabolites. This acid carries the apoptosis of cancer cell. SCFAs promote acidic environment in intestine and inhibit the production of secondary bile acids (29) (35).

CLA (conjugated linoleic acid) are able to suppress cancerous colon cells proliferation, by replace the arachidonic acid with linoleic acid and interfere in activity of lipoxygenase. Activity of CLA are depends on dose. When the Probiotics are consumed they produce fatty acids and promote anticancerous activity (36).

- **Modulate the physiochemical condition**

Apoptosis is programmed cell death event, pathogenic organisms having capacity to disturb the apoptosis and cause the cancer. Probiotics can regulate apoptosis. CRC patients suffered from the intestinal issues like acidity, viscosity etc. Probiotics can modify this by inhibit the cancerous event (29). Probiotics bacteria like *Lactobacillus* and *Bifidobacterium* produce acids like lactic acid and acetic acid which can lower the pH and inhibit pathogenic microorganisms (37).

- **Decrease inflammation in intestine.**

Probiotics stimulate anti-inflammatory substances, anti cancer compound and antioxidant components, it can affect the immune responses. Sometimes, Probiotics are also used for abnormal immune system related disease **(38)**. *Lactobacillus* interfere with the interleukins and reduce the inflammation.

SCFAs are also modulate the immune system and affect the inflammatory system by interfering with the signaling protein G. immune system is also prevent the tumor progression and control the tumor cell by interact with immune cells lie NK cell, B cell, T cell, Macrophage etc **(39)**.

Acetic acid and propionic acid also reduce inflammation, because they having capacity to inhibit the activations of kappa B factor and inflammatory cytokines. Propionic acid regulate cell apoptosis and cytokines, it also role as a energy source for colon cell **(29)**.

- **Affect the harmful enzymes as well as deactivate the carcinogenic component.**

Enzymes like azoreductase, beta-glucosidase, nitroreductase which are harmful and promote carcinogenic compound. Beta-glucosidase carried out hydrolyze of glucorinase. Probiotics produce compounds lie saromycin, neocarcinomycin, chromocin which role as a anticancerous compounds **(29)**, **(39)**, **(40)**.

The microorganisms like *Bacteroids*, *Clostridium*, *Salmonella*, *Staphylococcus*, *Enterococcus*, are produce enzymes like nitroreductase, azoreductase from the dye, raw meat, drug and aromatic nitro compounds, at the end it generate the toxic amines. Some genus like *Escherichia*, *Enterobacter, Streptococcus* increase the production of acetaldehyde which role as carcinogen **(29)**.

Lactic acid producing microbes having capacity to produce compounds which reduce the activity of carcinogenic compounds, deactivate carcinogen and antioxidant enzymes. *Lactobacillus* can reduce the effect of superoxide dismutase, glutathione S transfer, glutathione reductase, catalase and glutathione peroxide. **(41)**. Probiotics protect the body from oxidative stress during CRC.

How to administrate Probiotics in body:

The Probiotics can administrate as a drugs, cytokines, enzymes as well as DNA **(42)**, this are the best and successful way highly used in treatment and prevention of colon cancer. Probiotics are used as a vector because of their range of tolerance to the environment of GI tract and also having strength to colonizing at mucosal surface and protect the colon by pathogenic microbes **(43)**. New concept to administrate Probiotics are "BIO-DRUG", in which genetically modified Probiotics are delivery directly in the intestine. It have low cost as well as simple way to administrate, having great potential to used in treatment and prevention of colon cancer.

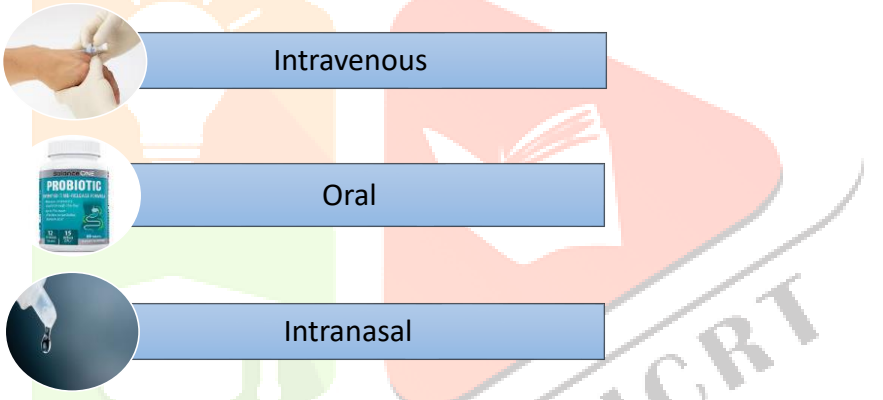

Figure 3: Administration ways of Probiotics in body

Potential doses of Probiotics in CRC:

Normal diet required 10^{9}-10^{12} bacterial cell with potential probiotic effect. After consumption of this diet it gives actions even after the week by increase the activity of macrophage, lymphocytes, cytokines and immunoglobulins in blood serum **(5)**, **(44)**.

When taking *Lactobacillus* and *Bifidobacterium* bacteria as Probiotics it required dose of 10^{10}-10^{11} CFU/day for a minimum 4-6 weeks to reduce CRC. The dose of Probiotics are not define because it varies with different strains of bacteria/Probiotics. Probiotic dose is must more than the amount of host microbiota. High number of Probiotics gives the beneficial effect on body/in CRC patient **(45)**, **(46)**.

Due to lack of specific data, we use AFSSA (Aureli's publication) **(46)**.

- ✓ The number of probiotic bacteria are high in concentration at different section of intestinal microbiota.
- ✓ The concentration of Probiotics are equal or greater than 10^{6}CFU/ml in small intestine and 10^{8}CFU/ml in large intestine.
- ✓ Concentration of microbiota of colon can be proposed because, it can expected that the bacterial flora is more active than lower levels.

Importance of Probiotics in Cancer treatment and prevention:

Marteau et al. studied that after the consumption of lactic fermented product it reduce the concentration of nitroreductase after three weeks. Bacterial enzyme activities are depended on the probiotic strain **(39) (47)**.

In other study, some Probiotics like *lactobacillus* shows the ability to increase the induction of 5-FU (5-fluorouracil) apoptosis. 5-FU used as a drug in chemotherapy, which cause diarrhea. Researcher compared the two patient of CRC. One patient supplemented with *Lactobacillus rhamnosus*. After the 24 weeks of chemotherapy they noticed, patient who received LAB did not have acute diarrhea **(48)**.

Bifidobacterium breve also protect the patients during chemotherapy against infection and changes of ecosystem of intestine **(49)**.

Lactobacillus rhamnosus gives the protection against the toxicity of radiation in radiotherapy patients **(50)**.

Lactobacillus casei modulate the immune response in mice against DMH-induced CRC **(51)**.

Lactobacillus acidophilus, lactobacillus casei and *lactic diacetylactis* DRC-1 which decrease the incidence, number and also the size of tumor **(52)**.

Future challenges in use of probiotics:

Most of the result of Probiotics are positive but sometimes bacterial strain which use as a probiotics are gives the side effect because of changes they may gives systematic infection deleterious metabolis activities, gene transfer and many other effects in immunocompromised person **(53)**. Therefore, if we have to use Probiotics for a long term then standardization are required by ensuring the side effects of Probiotics strains **(54)**.

Makarova et al. shows that Probiotics carried out adaptation in high nutrition, and lactobacillus reduce their size of genomeas a result of evolution **(55)**. Because of the pseudogenes in LAB which indicates the decay process of their genome.

Some stress condition also allow probiotic microbes to adapt at extreme condition that affect stress related genes and other evolutionary changes **(54)**. Stress condition induce mutagenesis to antibiotics resistance and bacterial pathogenesis. While stress effect on probiotics are only sometimes examine. LAB used as a bacteriostatic and bactericidal for food spoilages and pathogen could from stress induced mutation. May this effect the functional properties of probiotic microbes **(55)**.

But the modifications are also required. All modifications are not harmful sometime it will be a beneficial. The negative modification of probiotics are give serious influence in immunocompromised person and children. for the long term use off probiotics adverse evaluation are also important like antibiotics resistance transmission to pathogen **(56)**. We have to fully understood the ecological balance of gut microbiota by applying genetically modified probiotics in clinical phases **(57)**.

Conclusion:

Based on review, it can concluded that probiotics can give positive influence on whole body. Probiotics have a medical significance due to beneficial effect on the human body and health. They are adversely used in treat and prevent many types of disease. Probiotics are worked on both locally and whole body. Outer supplements of probiotics can modify the environment of gut and gives the protections to the body from pathogens. The effect of probiotics are depends on the bacterial strain, different strain gives different effect, because all the bacterial strains having different properties. There are many different mechanisms by which probiotics can reduce or prevent the colon rectal cancer. Many promising result are obtained which indicates the potential of probiotics. Therefore, this is important to do more research on anti-cancerous properties of probiotics of specific strains and their specific mechanisms. In additional, clinical trials should be continuously conducted either randomized or blinded to obtain approval from the medical community and validate the potential of probiotics as alternative therapy of chemotherapy or radiotherapy. We can use a probiotics as a gifting tool for cancer treatment and prevention.

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