Correlation Between Reactive Oxygen Species and Synbiotics for Effective Treatment of Cancer

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4.1 Introduction

Cancer is the third most prevalent related cause of death in the world, according to the National Cancer Institute. The World Health Organization estimates that around 27 million new instances of cancer will be diagnosed worldwide by 2030, resulting in the death of 17 million people. In the future, the World Health Organization predicts that approximately 75 million people would be afflicted by cancer in the United States. Furthermore, in addition to genetics and lifestyle factors, the etiology of colorectal cancer is complex and includes a combination of environmental and genetic factors that may cause changes in the intestinal microenvironment that result in carcinogenesis. Recent years have seen an increase in the interest in dietary methods for the prevention of cancer particularly when it comes to dietary restrictions and modifications. There have been numerous studies in clinical and epidemiological settings that have demonstrated the therapeutic effects of various nutrients and food constituents, such as calcium and selenium. Pericleous et al. (2013) suggested the roles of nutrition in the development of cancer, diet with high vitamin D content, n-3 fatty acids and digestible fibre may protect against colon cancer (Pericleous et al. 2013; Wu et al. 2018; Yang and Yu 2018). Extrinsic (i.e., environmental) factors such as infectious agents, antibiotic administration,

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high-fat diets, red meat consumption, and a lack of fiber intake, on the other hand, have a considerable impact on cancer risk (varying from 10% to 30%) (Wu et al. 2016).

Furthermore, all of these components have been shown to have an effect on the gut microbiota and cause dysbiosis, which is defined as disturbances of commensal communities that can result in a lack of immunological education in the host and the development of immune-mediated illnesses as a result of this lack of immunological education. The term dysbiosis refers to a state of affairs in which beneficial microorganisms have been eliminated, pathobionts or potentially hazardous microorganisms have multiplied, and total microbiological diversity has been eliminated (Almeida et al. 2018). A new study has discovered that patients with colorectal cancer have all three types of dysbiosis, according to the findings. The production of helpful metabolites by a healthy gut microbiota is one of the ways in which they can exert their anticancer benefits. One approach is by functioning as vitamins and as a source of energy. In addition to having antioxidant and anti-inflammatory effects, these beneficial metabolites can also control intestinal barrier function and serve as a source of energy. There is evidence that the gut microbiota of cancer patients can directly promote tumorigenesis; for example, fecal samples from cancer patients have been reported to produce intestinal carcinogenesis in germ-free mice and conventional mice when given to animals using a gavage procedure (Wong et al. 2017).

While prebiotics (nondigestible food ingredients that promote the growth of beneficial resident bacteria) are linked to the development of precancerous colonic lesions, the consumption of probiotics (living organisms believed to have a beneficial effect on health) is linked to the development of precancerous colonic lesions (Pool-Zobel 2005). Precarcinogenic food compounds can bind to synbiotics, reducing the production of bacterial enzymes that hydrolyze them, and reducing intestinal inflammation. Clinical trials have shown that synbiotics (a combination of probiotics and prebiotics) has a synergistic protective effect against the development and progression of cancer. Bacteria colonizing the intestine has been a hot topic recently, with many researchers questioning whether or not they have a role in cancer formation. When people with healthy gut microbiota compare their samples to those from people with colorectal cancer, it has been found that dysbiosis is a risk factor. Cancer cannot be linked empirically to a single pathogen, hence it is more likely caused by a host's interaction with an unbalanced gut microbiota, a condition known as dysbiosis, than the other way around (Bakhtiar et al. 2013).

It is estimated that the human intestinal microbiota contains trillions of bacteria, all of which colonize and disperse themselves at specific places in the body, where they form complex communities. Those that appear in the colon are the most numerous (approximately 10 microorganisms/g of intestinal content). The gastrointestinal tract contains helpful bacteria that are both locally and systemically useful in that they regulate intestinal homeostasis and neuromuscular function of the gastrointestinal tract (Sobhani et al. 2011). A possible mechanism by which the intestinal microbiota can interfere with the carcinogenic process is because of its potential to stimulate host immune responses, alter tumor cell metabolism, and govern cell death

and proliferation, among other things. Absorption and separation of bile acids are made easier as a result of this process, which has been found to enhance oxidative stress in experimental animals, damage DNA, and contribute to mitochondrial membrane instability. Probiotics are the most commonly utilized method of changing the intestinal flora. The microbiota and the host benefit from probiotics.

According to the American Cancer Society, research has shown that nondigestible food components known as prebiotics can help prevent cancer by encouraging the growth of good bacteria and the proper functioning of the colonic microbiota. When probiotic bacteria multiply, short-chain fatty acids (SCFAs) are produced in varying amounts, which is why they are beneficial. Probiotics and prebiotics alone may not be as effective in preventing cancer as synbiotics, which combine the two. Researchers found that combining a starch-resistant prebiotic with the probiotic Bifidobacterium lactis dramatically increased the mortality of colon cells in rats exposed to a carcinogenic toxin. To lessen the danger of side effects or to treat a wide range of disorders, Tárraga López et al. (2014) claim that natural alternatives to synthetic medications are becoming increasingly popular.

Probiotics and synbiotics may be useful in reducing cancer risk, particularly in the case of colorectal cancer, which has a high death rate around the world and is an aggressive tumor (Cruz et al. 2020). Disruption of the gut microbiota can lead to poor host health and the start of disease, which is why it is so important for human body homeostasis. Researchers are excited about the potential of probiotics in the treatment of colorectal cancer, and these microbes have shown their ability to aid in the process. The specific impacts of biological responses connected to colorectal carcinogenesis, particularly those relating to intestinal microbiota composition and changes caused by colorectal cancer, are not well understood. Microbes associated with cancer patients' mucosa differ dramatically from those of healthy individuals. Among other things, the microbiota of patients with colorectal cancer tends to become more diverse as the disease advances (Cruz et al. 2020). To find out if probiotics and synbiotics have a place in the fight against cancer, as well as to learn more about the underlying mechanisms that contribute to the disease's progression, this review was carried out. Having a healthy gut microbiome is critical to general health.

4.2 Reactive Oxygen Species (ROS) Formation

Molecules and free radicals generated by molecular oxygen are known as "reactive oxygen species" (ROS). The production of oxygen-based radicals is a problem that confronts all aerobic creatures. Aerobic respiration, mitochondrial electron transport, or metal-catalyzed oxidation can all produce these compounds, which can lead to oxidative stress. All aerobic creatures require this process in order to survive. While ROS production and ROS removal are now balanced, there are a wide range of defense mechanisms in place to meet this need. Oxidative stress is a condition in which the body's oxidative capacity is being strained (Bergqvist et al. 2020). Cells use a range of defensive mechanisms to fight ROS. Superoxide dismutase (SOD) can

act as a catalyst in a process to produce H_2O_2 and oxygen from two super oxide anions ($O_2^{-\bullet}$)

4.2.1 Types of ROS

Oxygen, oxygen radical$^{\bullet}$, hydrogen peroxide, and hydrogen peroxide are the most frequent ROS. When in its ground state, oxygen has two unpaired electrons with parallel spin, making it a paramagnetic molecule that is unlikely to interact with organic molecules until activated. Oxygen molecule can be activated using any of the following two approaches: Step-by-step monovalent reduction and absorbing enough energy to reverse an unpaired electron's spin are two ways to do this. There are two ways to make O_2: the first is to add oxygen to the air, and the second is to decrease it to O_2, H_2O_2, and OH (Bergqvist et al. 2020). The chloroplast, mitochondria, and peroxisomes are the only plant cell compartments where reactive oxygen species (ROS) can be produced continuously during aerobic metabolism. Moreover, a new study has shed light on the apoplast's importance as a generator of reactive oxygen species, as recently discovered data indicated (ROS). As long as there are suitable conditions, ROS production continues at a steady rate. To protect themselves from injury, they are scavenged by a variety of antioxidative systems (Sredoja Tisma et al. 2021).

Oxygen in the biradical state has a spin that is parallel to the spin of the atom's nuclei. Singlet states are formed when enough energy is absorbed to reverse one of the unpaired electrons' spin, creating an electron pair with the opposite spin. By participating in processes involving the simultaneous transfer of two electrons, O_2 is able to break past the spin barrier (divalent reduction). ROS are primarily produced in plants by the mitochondria, which are the most abundant organelle in plants, followed by chloroplasts and peroxisomes. The endoplasmic reticulum, cell membrane, cell wall, and apoplast are only a few examples of secondary sites. Under diverse environmental stress circumstances such as salt, drought, cold, heavy metals, UV irradiation, and so on, ROS family members play a vital dual function in maintaining normal cellular homeostasis.

Oxidative damage can occur as a result of their role as secondary messengers in a number of physiological processes (Yang et al. 2021). The breakdown of biomolecules including pigments, proteins, lipids, carbohydrates, and DNA occurs as a result of cellular damage, and this results in the death of the plant's cellular structure and function. Researchers found that plants have evolved a robust antioxidant apparatus with two arms, including SOD (superoxide dismutase), DHR (dehydro-ascorbate reductase) works together to scavenge ROS (Yang et al. 2021). The delicate equilibrium between ROS formation and ROS scavenging is disrupted by several stress conditions, such as salt, aridity, high temperatures, heavy metals, and pathogen infection, among others. The severity and duration of stress episodes, as well as the plants' ability to quickly react to fluctuating energy balances, are all important considerations for plants' survival (Wang et al. 2017). Residual oxygen

species are believed to be produced in plants using only 1–2% of the oxygen available to the ROS.

ROS were formerly thought to be primarily produced by mitochondrial metabolism. This is contrary to conventional opinion, as research has shown that NADPH-oxidase enzymes create a significant amount of ROS in people. There are many different reduction stages toxic reactive oxygen species (ROS) might go through before they affect healthy cells. To ensure the survival of all cells in the body, the detoxification of reactive oxygen species (ROS) is essential. Numerous defense systems had to be developed in order for live organisms to survive in the oxygen-rich cellular environment. The purpose of these defense mechanisms is to protect against reactive oxygen species (ROS). An imbalance between ROS production and cell ability to rapidly detoxify or recover from ROS-induced damage is referred to as oxidative stress.

Oxidative stress, the outcome of an imbalance between the creation and detoxification of reactive oxygen species, leads to cellular failure (ROS). ROS causes lipid peroxidation, nucleic acid alterations, and protein aberrations in biological macromolecules. Their formation has been related to atherosclerosis (ischemic heart disease), diabetes, and the development of carcinogenesis or liver disease. In order to maintain proper cell signaling, several radical scavenging enzymes are considered to keep ROS levels within the cell below a certain threshold (Woelk and Snyder 2021). An increase in ROS synthesis can result in excessive cell signals and damage to critical components of the signaling pathway, but there is a limit to the quantity of ROS that can be created. ROS has the potential to permanently harm vital macromolecules. The –SH group in the protein-bound and non-protein thiol compounds provides a cellular reducing and protective agent against a wide spectrum of hazardous substances, including most inorganic contaminants. The initial line of defense against oxidative stress is often thiolactone.

4.3 Carcinogenesis

Carcinogenesis is the process of transforming normal cells into cancerous ones through uncontrolled proliferation and genetic abnormalities (Pu et al. 2020). Carcinogenesis is usually divided into phases. A normal cell becomes a tumor cell after irreversible changes to its DNA (deoxyribonucleic acid) in the nucleus; tumor promotion occurs when a clone of initiated cells proliferates abnormally; and tumor progression occurs when precancerous lesions become malignant lesions due to initiated cell proliferation. Cancer cells eventually acquire features that distinguish tumors from healthy tissue (Flemer et al. 2018). These include the ability to proliferate, resistance to apoptosis (programmed cell death), and angiogenesis (tumor-specific vascular growth) (dissemination through the blood or lymphatic system to distant organs). Toxic substances damage chromosomes and genetic make-up (DNA). This is especially true of several substances to which employees are often exposed. Throughout a cell's life, DNA gets attacked, but the repair processes usually heal the damage.

However, failure or suppression of essential gene repair processes can cause or exacerbate cell transformation and thus carcinogenesis, especially when environmental factors are involved. When a cell splits, its genetic material is passed on to the daughter cells (Liu et al. 2020). Unrepaired DNA lesions can cause genome-wide changes like chromosomal rearrangements or gene mutations. Oncogenes and tumor suppressor genes are required for cell growth, division, differentiation, and death. This allows for balanced cell division. Mutations in these genes promote the growth of a clone of abnormal cells. To finish the process of carcinogenesis takes years or perhaps decades.

4.3.1 Stages of Cancer and Its Management vis a vis Chemoprevention Cum Gut Microbiota

Oncogenic pathways are needed to understand cancer etiology and pathology. Gut microbiota and carcinogenesis: environmental and genetic factors (Hekmatshoar et al. 2019). The indirect bacterial process of oncogenesis is shown in the course of chronic inflammation caused by bacterial infections. The microbiota can activate the transcription factor nuclear factor-kB (NF-kB) and hence contribute in the formation of malignant tumors by producing inflammation mediators such as TNF-a and IL-1. Also, metabolites or toxin generated by bacteria can initiate bacterial oncogenesis. Previous research has connected gut microbiota to cancers such gastric cancer, colorectal cancer, and hepatocellular carcinoma (HCC).

All of these carcinogenic processes share the same trait: microbial metabolite production (Liu et al. 2020). SHP2 and PAR1/MARK interact with *H. pylori* CagA proteins to promote carcinogenesis. *Bacteroides fragilis* is an opportunistic pathogen. Colorectal cancer can be caused by toxic *B. fragilis* (ETBF), one of two *B. fragilis* subtypes (CRC). When *B. fragilis* toxin is present, decreased spermine oxidase activity causes reactive oxygen species (ROS) and indirect DNA damage. *Pasteurella multocida* toxin, CDT, and IPPPD have also been linked to cancer risk (IpgD). All of these factors may affect cellular responses, increasing the risk of cancer (Tsvetikova and Koshel 2020). A healthy gut microbiome profile is thought to be adequate for a healthy microbiota. Aiming for dysbiosis may improve the prognosis and reduce negative effects of various anticancer drugs (Fig. 4.1).

4.4 Gut Microbiota and Cancer

Recent research shows that gut microorganisms impact a host's overall health. Various metabolites and bioproducts produced by gut bacteria safeguard the host and gut homeostasis. In contrast, pathological dysbiosis may increase the number of microbiota subpopulations that produce toxins that can cause inflammation and cancer. Gut microbial interactions can alter the host's immune system and gut epithelium (Yang et al. 2019).

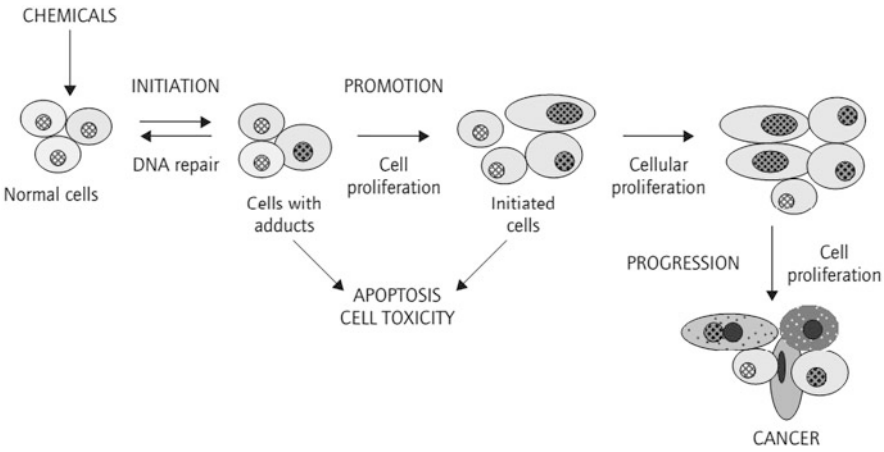

Fig. 4.1 Steps involve in carcinogenesis

Probiotics, or intestinal microorganisms, have been shown to protect against cancer growth. Probiotics are currently being examined to determine if they can help dysbiosis-prone cancer patients undergoing chemotherapy and radiotherapy. Three recent research suggest that certain gut-dwelling species may benefit anticancer treatment. Even if these treatments are effective of suppressing the progression or even killing some types of cancer cells, there remain limitations due to developed resistance and unpleasant side effects (Winkler et al. 2014).

The human epithelia contain a range of microorganisms, the most common being commensal bacteria found in the gastrointestinal tract, collectively known as the human microbiota. High-throughput sequencing has made it possible to pinpoint the gut microbiota's composition. Healthy people have the following bacterial types: non-Actinobacteria, proteobacteria, or firmicutes microorganisms. Many cancer drugs may benefit from better gut microbiota control, according to recent research linking gut microorganisms and treatment results, including reduced cytotoxic activity (Chang et al. 2020).

4.4.1 Microbiota and Chemotherapy

Chemotherapy is one of the most effective systemic cancer treatments today. Chemotherapeutic drugs that target DNA, topoisomerase, or tubulin can stop cancer cells from growing and multiplying. Despite this, there are unavoidable adverse effects due to the lack of specific chemotherapeutic targets. It was eventually discovered that gut microorganisms and cytotoxic drugs interact in two ways. Chemotherapy reduces the number and diversity of bacteria in several preclinical studies. A decrease in *Lactobacillus* and *Bifidobacterium* and an increase in *Escherichia coli* (*E. coli*) and *Staphylococcus* has been observed in clinical studies. The changed microbiota composition causes an inflammatory response and reduces

barrier function, exposing the host to pathogens (Schirmer et al. 2016). The microbiota in the stomach can affect the efficiency of chemotherapy in two ways. Many anticancer drugs that are given orally or injected into the body rely on gut microbes to become active. In CRC treatment, intravenous carboxylesterase converts CPT-11 (irinotecan) to SN-38.

The drug's active ingredient prevents DNA ligation, causing single and double strand breaks. UDP-glucuronosyl transferase then detoxifies it (UDP-transferase). It was shown that SN-38 levels in feces increased from 2% to 12% of the dose when deconjugation by gut microbiota generated beta-glucuronidases occurred. According to the research, microbes have a vital role in drug. Alternatively, gut bacteria may help synthesize chemicals that block an enzyme used in drug detoxification, causing more severe adverse effects. When rats are given 5-FU with Sorivudine, Sorivudine is transformed to bromovinyluracil, which further inhibits the 5-FU detoxifying enzyme dihydropyrimidine dehydrogenase. This is a prevalent topic in 5-FU toxicity studies. 5-FU, which aids in DNA replication, can cause diarrhea and even decrease of leukocyte and platelet counts if used long term and in high doses (Klaassen and Cui 2015). This conversion occurred solely within the human body and was proved by experiment to be due to gut microbiota species, revealing the crucial role gut microorganisms play in chemotherapy-induced harm. The gut microbiota may increase the toxicity of chemotherapy treatments while simultaneously helping them fight cancer. Increasing the expression of reactive oxygen species-producing enzymes (ROS) (Woelk and Snyder 2021). Defensively, the gut microbiome may help chemotherapy work better and less harmful. Gene silencing can increase the expression of ROS-generating enzymes. ROS can damage DNA and trigger apoptosis in tumor cells when employed as a chemotherapeutic. Less expression of Nox1 and Cybb genes coding for NADPH oxidase 2 genes in germ-free mice or mice treated with an antibiotic cocktail (ABX) may minimize anticancer effects (Nox2). Enzyme compartment-specific superoxide dismutases (SOD) can produce H_2O_2, causing DNA damage in tumor cells and necrosis (Fig. 4.2) (Chang et al. 2020).

4.5 Synergy of Probiotics and Prebiotics and Mode of Action

In silico evaluation and metagenomics have been used to study a quiet of useful and important diverse group of microbes that reside in the human gut microbiota. Currently, the study on gut microbiota is continually gaining attention as their role in protecting against diseases are significant. Prebiotics and probiotics are two important food components that are needed in the human gastrointestinal tract. The human gastrointestinal track can house viable microbes which when ingested can help prevent against some pathological conditions, such organisms are widely regarded as probiotics. These microbes found in some foods, thereby interacting with the indigenous colon organisms limiting the concentration of the pathogenic ones (Sanders et al. 2019). In other hand, prebiotics are compounds or structure which supports the growth of probiotics.

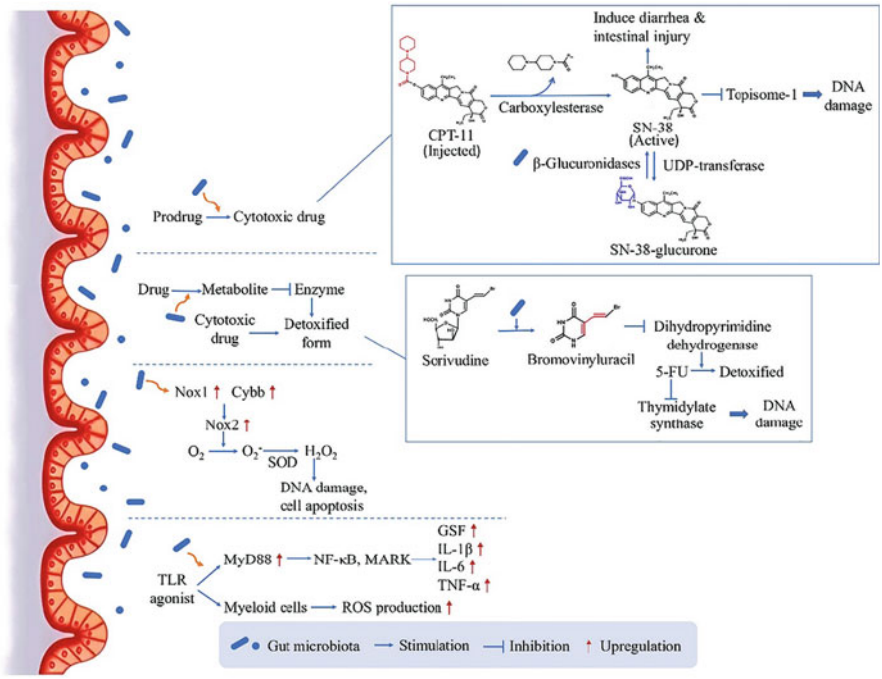

Fig. 4.2 Drug pharmacokinetics and ROS generation are directly influenced by bacteria. The gut microbiota can directly influence medication conversion and gene transcription, resulting in either an increased therapeutic impact or an increased adverse effect (Li et al. 2021)

Consumption of some foods which includes butter, yogurt, and milk and other fermented foods have been studied to be rich in probiotics, the discovery of such food is describe through a phenomenon called probiosis. Probiosis is a term used to describe the correct consumption of fermented products with cultures of beneficiary microbes (Mtasher et al. 2018). Fermented foods have long taken as a nutritional food, but off recent their importance in clinical settings. Obstruction of the normal floral of the gut is accompanied by the overgrowth of pathogenic microbes leading to significant loss diversity of important gut microbes and as such inflammatory response is built up by the host causing the disease conditions (Molehin et al. 2022). Prebiotics exclusively enhances the proliferation of beneficial bacteria in the gastrointestinal track. Live organisms such as probiotics confers a health importance on the host when taken appropriately in the right food components. Probiotics mode of action is not fully outlined and understood, but their survivals in the intestine brings about stability of the intestinal ecosystem. The criteria for optimal activities of probiotics is believed to be depending on the number or population of the viable cultures of medical significance and the bio-efficiency of the prebiotics which helps stimulate their growth (Patel et al. 2015).

The probiotic community may include on or more microbial strains which may include *Bacillus* spp., *Enterococcus* spp., *Lactobacillus* spp., *Pediococcus* spp., and *Streptococcus* spp. Since microorganisms are fully involved in both probiotics and prebiotics, the assessment of such strains for safety is very important weather which strains are being optimized to maximized it health-related positive effect. However, the mechanism of actions of probiotics is not fully understood, but it has been reported that they are capable of surviving the harsh environment of the alimentary canal while offering a beneficiary effect on their host (Anadón et al. 2014). The presence of these beneficiary microorganisms has been studied to improve digestion and enhancing metabolic and immunological processes.

Therefore, properties of probiotics are to enhanced health and increase productivity of animals. Microorganisms with probiotic capacities are well structured to adhere to epithelial cells subsequently blocking or hindering the binding of their receptors to the epithelial cells. The blockage by probiotic bacteria is as a result of competition and production of anti-adhesive effect leading to activation of mucin (a complex glycoprotein mixture). Many scientific studies have shown how different lactobacilli glycoprotein promotes their subsequent binding to the mucosal membrane mediating their surface attachments layer (González-Rodríguez et al. 2012).

There are many groups of organisms that have been explored and used as probiotics. It is important to note that many of these genera have similar biochemical, physical, and metabolic characteristics. The Lactobacillus group are the most profound of all the probiotics, they are Gram-positive rod-shaped microorganisms possessing the ability to produce an organic acid called lactic acid. These group of organisms are regarded as friendly microbes as their colonization proved to be beneficiary and nutritional (Table 4.1).

Probiotic bacterium plays very important role in several health challenges and performance. Some of the importance include their therapeutic effect, well-structured microbial concentration in the intestine, and other aiding several immunomodulatory and metabolic responses (Anandharaj et al. 2014). Despite several colonization of microbes in the colon, there are several idea requirements for being a probiotic bacterium. Such requirement includes the following (Behnsen et al. 2013)

1. For an organism to be regarded as probiotic, they should give a positive effect on the host gastrointestinal tract.
2. Such organisms must strive in the presence of acidic nature of the stomach while also resisting the antimicrobial effect of bile.
3. The binding to their host mucosal surfaces must be fast and firm without easy of obstructions.
4. They must be able to propagate themselves easily and faster.
5. They must be capable to exclude pathogenic invasion by blocking the adherence of the pathogens with the epithelial tissues.
6. Even when heavily populated, they must be safe, noninvasive, nonpathogenic, noncancerous to their host.

Table 4.1 List of commonly used microbes as probiotics

Genus	Species
Lactobacillus spp.	*acidophilus* *plantarum* *rhamnosus* *paracasei* *fermentum* *reuteri* *johnsonii* *brevis* *casei* *lactis* *delbrueckii gasseri*
Bifidobacterium spp.	*breve* *infantis* *longum* *bifidum* *thermophilum* *adolescentis* *animalis* *lactis*
Bacillus spp.	*coagulans*
Streptococcus spp.	*thermophilus*
Enterococcus spp.	*faecium*
Saccharomyces spp.	*cerevisiae*

7. With other nonpathogenic bacteria, they must be able to form a conglomerate of balance normal flora.
8. They must be durable and have capabilities to withstand commercial processing.

4.6 Antioxidation Properties of Probiotics

Many scientific reports have confirmed that probiotics is capable of lowering lower the onset and severity of diarrhea, aside from that, the presence of probiotics in a compactible host help regulate both the active and passive immunity while preventing tumor cells proliferations and decreasing metabolism of ammonium containing foods and pro-cancerogenic enzymes in the stomach (Mishra et al. 2015). It has been studied that probiotic has resolved various metabolic processes such as diabetes and obesity through modifying intestinal microorganisms (Rad et al. 2016). Oxygen is regarded as an important factor negatively influencing the survival of anaerobic organism of any kind. The oxygenic environment is thought to stimulate the production of toxic end product stimulated by oxygen.

Oxidative stress is biochemically described as a condition which disturbs the prooxidant-antioxidant balance within the cell. As a result, DNA hydroxylation, denaturation of protein, peroxidation of lipid, and untimely programmed cell death are all being initiated following the oxidative stress. As such, oxidative stress increases the intracellular oxygen expenditure and radicals leading to reactive

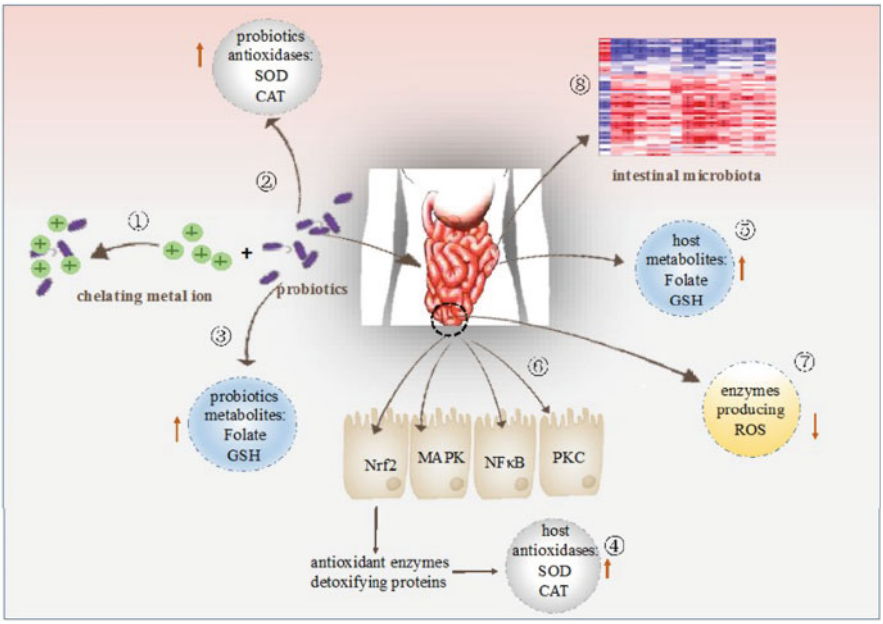

Fig. 4.3 Mechanism of antioxidative modulation by probiotics (Wang et al. 2017)

oxygen species (ROS), superoxide anion radicals, and hydrogen peroxide (Schieber and Chandel 2014). Most living organisms are programmed to defend antioxidant imbalance many of which are enzymatic in nature such as superoxide dismutase, and some are non-enzymatic based such as Vitamin C and E, all which are not enough for antioxidative defense (Mishra et al. 2015).

Most studies on probiotics and prebiotics have mainly focused their anti-diarrhea potentials, immune-stimulating factors, immunomodulation, and their ability to reduce unpleasant metabolites in the body while less focusing on their anticancer and antioxidative potentials (Mishra et al. 2015). The antioxidative potential of probiotics is currently gaining focus. Recently, cultures of *Bifidobacterium animalis* were observed to scavenge superoxide anion and hydroxyl radicals in vitro while encouraging antioxidase activities. Oxidative stress of type 2 diabetic patients has been studied to recede following the ingestion of probiotics (Fig. 4.3) (Wang et al. 2017).

Probiotic organisms scavenge free radical through various means. Probiotic microbes can act as chelators such as penicillamine and ethylene diamine tetra-acetic acid (EDTA) which enables to capture metallic ions subsequently preventing them from further oxidation. Cellular apparatus responsible for these chelating potentials are not well understood (Wang et al. 2017). Since probiotic microbes are living entities themselves, they possess their own antioxidative system. One of its well-studied antioxidative systems are the antioxidant enzymatic apparatus observed are superoxide dismutases (SOD).

Furthermore, probiotics can stimulate antioxidases from the host antioxidative apparatus (Wang et al. 2017). Probiotics can also serve as antioxidant metabolite through production of various metabolite such as folate, butyrate, and glutathione. It is important to note that folate is a very important vitamin needed during DNA replication, optimization of DNA repair mechanisms, and DNA methylation (Wang et al. 2017).

4.7 Effective Management of Cancer Through Symbiotics

There are investigations regarding the combine use of probiotics and prebiotics in the management of cancer. Many anticancer activities of probiotics such as *Lactobacillus* spp., *Bifidobacteria* and many others have been studied to have antimutagenic potentials due to the fact that they are capable of metabolizing and inactivating mutagenic compounds. In other studies, the anticancer effect of probiotics is also strengthened by their ability to inhibit procarcinogen which transforms to active carcinogens, reduction and inactivation of mutagenic compounds, and the subsequent reinforcement and optimization of functions for the immune system (Fig. 4.4) (Soccol et al. 2010).

The antitumor potentials of probiotics are based on the following functions which are: upregulation of metabolic activity of the microbes in the intestine, modification of microbial population in the intestine, production of short chained fatty acids as well as conjugated linoleic acids both which have anticancer effect, inhibition of abnormal cell proliferation coupled with immunomodulation potentials (Śliżewska et al. 2020). Imbalance in the population and varieties of microbes found in the intestine may give room for pathogenic organisms leading to dysbiosis which is termed as excess of pathogenic microbe invasions. When these conditions are not properly curtailed, they cause severe inflammation in the system which could lead to

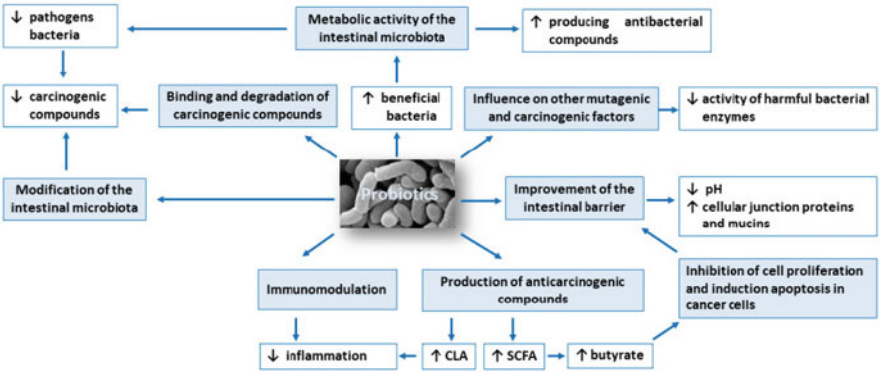

Fig. 4.4 Flowchart showing possible mode of actions of probiotics on colon cancer (Śliżewska et al. 2020)

accumulation of carcinogenic compound thus increasing the likelihood of colon cancer (Dos Reis et al. 2017).

Probiotic microbes compete with their pathogenic counterpart restricting their attachment with mucosal membranes through the development of complex and quorum sensing triggered structured called biofilm (Ohland and Mac Naughton 2010). Biofilms are formed through complex interaction within diverse genetic population where individual microbes contribute their extracellular compound by specific command called quorum sensing. Such extracellular substance includes protein, capsules, polysaccharides, and phospholipids among many others. The probiotics presence meaningfully reduces the menace of postoperative difficulties which could be anastomotic leakage, mechanical ventilation, and infections (Śliżewska et al. 2020).

In some cases, nonpathogenic microbes may covert some found components into carcinogenic compounds. For example, the ability of some microbes to produce enzymes such as nitrate reductase, azoreductase, and beta-glucosidase all which have been studied to be capable of bio-transforming heterocyclic and polycyclic aromatic compounds including bile acids into ammonia, phenols, synthetic aglycones, cresols, and N-nitroso compound all which are potential hazards to the biological system. In more severe cases, such enzymes can covert these compounds into active carcinogens (Zhu et al. 2013).

Probiotic microbes can challenge this bio-transformation by changing the microbial metabolism through modulating the actions of the enzyme concerned. *E. coli*, *Clostridium* spp., and other related microbes have higher enzyme activities required for synthesis of carcinogenic compounds, probiotic bacteria are capable of reducing the pathogenic population of such bacteria and consequently decreases the initiation of carcinogenesis (Śliżewska et al. 2020). Lactic acid bacteria (LAB) control the population of other microbes in their immediate environment by producing organic acids. Organic acids are considered as one of the major acids that helps inhibit the propagation of pathogenic microbes. The most important compounds produced by LAB are the lactic acids, acetic acids hydrogen peroxide and bacteriocin all which can inhibit the growth of pathogens with high selective toxicity (Śliżewska et al. 2020).

References

Almeida CVD, de Camargo MR, Russo E, Amedei A (2018) Role of diet and gut microbiota on colorectal cancer immunomodulation. World J Gastroenterol 25:151–162

Anadón A, Castellano V, Martínez-Larrañaga MR (2014) Regulation and guidelines of probiotics and prebiotics. In: Ötles S (ed) Probiotics and prebiotics in food, nutrition and health. CRC Press, LLC Taylor & Francis Group, Boca Raton, FL, pp 91–113. ISBN 978–1–4665-8623-9

Anandharaj M, Sivasankari B, Parveen RR (2014) Effects of probiotics, prebiotics, and synbiotics on hypercholesterolemia: a review. Biology 2014

Bakhtiar SM, LeBlanc JG, Salvucci E, Ali A, Martin R, Langella P, Chatel JM, Miyoshi A, Bermúdez-Humarán LG, Azevedo V (2013) Implications of the human microbiome in inflammatory bowel diseases. FEMS Microbiol Lett 342:10–17

Behnsen J, Deriu E, Sassone-Corsi M, Raffatellu M (2013) Probiotics: properties, examples, and specific applications. Cold Spring Harb Perspect Med 3(3):a010074

Bergqvist C, Safi R, El Hasbani G, Abbas O, Kibbi A, Nassar D (2020) Neutrophil extracellular traps are present in immunecomplex-mediated cutaneous small vessel vasculitis and correlate with the production of reactive oxygen species and the severity of vessel damage. Acta Derm Venereol 100:adv00281

Chang CW, Lee HC, Li LH, Chiang Chiau JS, Wang TE, Chuang WH et al (2020) Fecal microbiota transplantation prevents intestinal injury, upregulation of toll-like receptors, and 5-fluorouracil/oxaliplatin-induced toxicity in colorectal cancer. Int J Mol Sci 21(2):386

Cruz BCS, Sarandy MM, Messias AC, Gonçalves RV, Ferreira CLLF, Peluzio MCG (2020) Preclinical and clinical relevance of probiotics and synbiotics in colorectal carcinogenesis: a systematic review. Nutr Rev 78:667–687

Dos Reis SA, Da Conceição LL, Siqueira NP, Rosa DD, Da Silva LL, Peluzio MCG (2017) Review of the mechanisms of probiotic actions in the prevention of colorectal cancer. Nutr Res 37:1–19

Flemer B, Warren RD, Barrett MP, Cisek K, Das A, Jeffery IB, Hurley E, O'Riordain M, Shanahan F, O'Toole PW (2018) The oral microbiota in colorectal cancer is distinctive and predictive. Gut 67:1454–1463

González-Rodríguez I, Sánchez B, Ruiz L, Turroni F, Ventura M, Ruas-Madiedo P, Gueimonde M, Margolles A (2012) Role of extracellular transaldolase from Bifidobacterium bifidum in mucin adhesion and aggregation. Appl Environ Microbiol 78(11):3992–3998

Hekmatshoar Y, Rahbar Saadat Y, Hosseiniyan Khatibi SM, Ozkan T, Zununi Vahed F, Nariman-Saleh-Fam Z et al (2019) The impact of tumor and gut microbiotas on cancer therapy: beneficial or detrimental? Life Sci 233:116680

Klaassen CD, Cui JY (2015) Review: mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. Drug Metab Dispos 43(10):1505–1521

Li W, Deng X, Chen T (2021) Exploring the modulatory effects of gut microbiota in anti-cancer therapy. Front Oncol 11:644454

Liu W, Zhang R, Shu R, Yu J, Li H, Long H, Jin S, Li S, Hu Q, Yao F et al (2020) Study of the relationship between microbiome and colorectal cancer susceptibility using 16SrRNA sequencing. Biomed Res Int 2020:7828392

Mishra V, Shah C, Mokashe N, Chavan R, Yadav H, Prajapati J (2015) Probiotics as potential antioxidants: a systematic review. J Agric Food Chem 63:3615–3626

Molehin OR, Elekofehinti OO, Ohunayo AS, Adetuyi OA (2022) Challenges in understanding the lung microbiota. In: Gupta G, Oliver BG, Dua K, Singh A, Mac LR (eds) Microbiome in inflammatory lung diseases. Springer, Singapore. https://doi.org/10.1007/978-981-16-8957-4_18

Mtasher AS, Abdulhussein AJ, Mutlag SH (2018) Probiotics and prebiotics. Int J Curr Res 10(11):75341–75352

Ohland CL, Mac Naughton WK (2010) Probiotic bacteria and intestinal barrier function. Am J Physiol Gastrointest Liver Physiol 298:807–819

Patel S, Shukla R, Goyal A (2015) Probiotics in valorization of innate immunity across various animal models. J Funct Foods 14:549–561

Pericleous M, Mandair D, Caplin ME (2013) Diet and supplements and their impact on colorectal cancer. J Gastrointest Oncol 4:409–423

Pool-Zobel BL (2005) Inulin-type fructans and reduction cancer risk: review of experimental and human data. Br J Nutr 93(Suppl 1):S73–S90

Pu LZCT, Yamamoto K, Honda T, Nakamura M, Yamamura T, Hattori S, Burt AD, Singh R, Hirooka Y, Fujishiro M (2020) Microbiota profile is different for early and invasive colorectal cancer and is consistent throughout the colon. J Gastroenterol Hepatol 35:433–437

Rad AH, Sahhaf F, Hassanalilou T, Ejtahed HS, Motayagheni N, Soroush AR, Javadi M, Mortazavian AM, Khalili L (2016) Diabetes management by probiotics: current knowledge and future perspectives. Curr Diabetes Rev 86:215–217

Sanders ME, Merenstein DJ, Reid G et al (2019) Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol 16:605–616. https://doi.org/10.1038/s41575-019-0173-3

Schieber M, Chandel NS (2014) ROS function in redox signaling and oxidative stress. Curr Biol 24: R453–R462

Schirmer M, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, Franzosa EA et al (2016) Linking the human gut microbiome to inflammatory cytokine production capacity. Cell 167(4):1125–36. e8. https://doi.org/10.1016/j.cell.2016.10.020

Śliżewska K, Markowiak-Kopeć P, Śliżewska W (2020) The role of probiotics in cancer prevention. Cancers (Basel) 13(1):20. https://doi.org/10.3390/cancers13010020

Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, Langella P, Corthier G, Tran Van Nhieu J, Furet JP (2011) Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One 6: e16393

Soccol CR, de Souza Vandenberghe LP, Spier MR, Medeiros AB, Yamaguishi CT, De Dea LJ, Pandey A, Thomaz-Soccol V (2010) The potential of probiotics: a review. Food Technol Biotechnol 48(4):413–434

Sredoja Tisma V, Bulimbasic S, Galesic Ljubanovic D, Galesic K, Morovic-Vergles J, Mitrovic J, Uchida K, Tatzber F, Zarkovic N, Jaganjac M (2021) The onset of systemic oxidative stress associated with the accumulation of lipid peroxidation product acrolein in the skin of patients with small-vessel vasculitis. Molecules 26:2344

Tárraga López PJ, Albero JS, Rodríguez-Montes JA (2014) Primary and secondary prevention of colorectal cancer. Clin Med Insights Gastroenterol 7:33–46

Tsvetikova SA, Koshel EI (2020) Microbiota and cancer: host cellular mechanisms activated by gut microbial metabolites. Int J Med Microbiol 310(4):151425

Wang Y, Wu Y, Wang Y, Xu H, Mei X, Yu D, Wang Y, Li W (2017) Antioxidant properties of probiotic bacteria. Nutrients 9(5):521. https://doi.org/10.3390/nu9050521

Winkler GC, Barle EL, Galati G, Kluwe WM (2014) Functional differentiation of cytotoxic cancer drugs and targeted cancer therapeutics. Regul Toxicol Pharmacol 70(1):46–53

Woelk CH, Snyder A (2021) Modulating gut microbiota to treat cancer. Science 371:573–574

Wong SH, Zhao L, Zhang X, Nakatsu G, Han J, Xu W, Xiao X, Kwong TNY, Tsoi H, Wu WKK et al (2017) Gavage of fecal samples from patients with colorectal cancer promotes intestinal carcinogenesis in germ-free and conventional mice. Gastroenterology 153:1621–1633.e1626

Wu S, Powers S, Zhu W, Hannun YA (2016) Substantial contribution of extrinsic risk factors to cancer development. Nature 529:43–47

Wu X, Wu Y, He L, Wu L, Wang X, Liu Z (2018) Effects of the intestinal microbial metabolite butyrate on the development of colorectal cancer. J Cancer 9(14):2510–2517

Yang C, Chen Y, Huang H, Fan S, Yang C, Wang L, Li W, Niu W, Liao J (2021) ROS-eliminating carboxymethyl chitosan hydrogel to enhance burn wound-healing efficacy. Front Pharmacol 12: 679580

Yang Y, Misra BB, Liang L, Bi D, Weng W, Wu W, Cai S, Qin H, Goel A, Li X et al (2019) Integrated microbiome and metabolome analysis reveals a novel interplay between commensal bacteria and metabolites in colorectal cancer. Theranostics 9:4101–4114

Yang Y, Yu J (2018) The association of diet, gut microbiota and colorectal cancer: what we eat may imply what we get. Protein Cell 9(5):474–487

Zhu Q, Gao R, Wu W, Qin H (2013) The role of gut microbiota in the pathogenesis of colorectal cancer. Tumor Biol 34:1285–1300. https://doi.org/10.1007/s13277-013-0684-4