Microbe-Induced Oxidative Stress in Cancer Development and Efficacy of Probiotics as Therapeutics in Preventing Its Onset and Progression

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Abstract

Within the metaorganisms, cross-communication between commensal organisms and the host is crucial for the maintenance of physiological homeostasis. At times, microbiota becomes accountable for breaching homeostasis by creating a micro-environment favoring uncontrolled cell growth. Chronic infection and inflammation act as inciting factors for reactive oxygen species generation promoting damage to DNA, proteins, and lipids. Oxidative stress activates a variety of transcription factors that in turn control the expression of several inflammatory cytokines and chemokines. Consecutive changes including altered cell growth, genetic instability, and inhibition of apoptosis create a proper carcinogenic milieu. Apart from the complicated side effects associated with prevailing anti-cancer therapies, their safety, stability, and affordability are in question. At present, significant immunomodulating properties of probiotic bacteria are being considered as a promising tool in cancer treatment. In addition, to boost the innate defense mechanisms of hosts, probiotics can act as antigenotoxic, anticarcinogenic, and antioxidative agents. In this chapter, the role of pathogenic microbes in oxidative stress-induced cancer and the effectiveness of probiotics as a future therapeutic strategy in preventing cancer onset and progression through manipulating intestinal microflora are highlighted.

Keywords

Cancer · Oxidative stress · Probiotics · Bacterial toxin · Inflammation · Dysbiosis · Protozoa-induced cancer

Abbreviations

4-HNE	4-Hydroxynonenal
8-OHdG	8-Hydroxydeoxyguanosine
8-oxo-dG	8-Oxo-2′-deoxyguanosine
ADH	Alcohol dehydrogenase
AID	Activation-induced cytidine deaminase
AMPK	Adenosine monophosphate-activated protein kinase
AMPs	Antimicrobial peptides
APC	Anaphase promoting complex
APRIL	A proliferation-inducing ligand
AQP3	Aquaporin 3
ATP	Adenosine triphosphate
AvrA	Avirulence protein A
BAD	BCL-2-associated death promoter
BAFF	B cell-activating factor
BAX	BCL-2 associated X
BCL-2	B-cell lymphoma 2
BER	Base excision repair
BFT	*B. fragilis* toxin

BLIMP	B lymphocyte-induced maturation protein 1
cagA	Cytotoxin-associated gene A
CD	Crohn's disease
CDKs	Cyclin-dependent kinases
CDT	Cytolethal distending toxin
CIDR	Succeeding cysteine-rich interdomain region
CLRs	C-type lectin receptors
CNF1	Cytotoxic necrotizing factor 1
COX	Cyclooxygenase
CRC	Colorectal cancer
CTCL	Cutaneous T-cell lymphoma
CTL	Cytotoxic T lymphocytes
CXCL	C-X-C motif chemokine ligand
CYP	Cytochrome P450
DC	Dendritic cell
DDR	DNA damage responses
DNA	Deoxyribonucleic acid
DNase I	Deoxyribonuclease I
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DSBs	Double-strand breaks
EBV	Epstein-Barr virus
ERK	Extracellular regulated kinase
ETBF	Enterotoxigenic *B. fragilis*
Etk/BMX	Epithelial and endothelial tyrosine kinase/bone marrow X
FOXO3a	Forkhead box O3a
GEC	Gingival epithelial cell
GI	Gastrointestinal
GPRs	G-protein-coupled receptors
GPX1	Glutathione peroxidase 1
HCC	Hepatocellular carcinoma
HDAC	Histone deacetylase
HIF-1α	Hypoxia-inducible factor 1α
HNE	4-Hydroxy-2-nonenal
HRE	Hypoxia response element
HSP	Heat shock protein
IARC	International Agency for Research on Cancer
IBD	Inflammatory bowel disease
IFN-γ	Interferon-γ
IgA	Immunoglobulin A
IL	Interleukin
JAK1/STAT3	Janus kinase 1/signal transducer and activator of transcription 3
JNK	c-Jun N-terminal kinases
LPS	Lipopolysaccharide
MALT	Mucosa-associated lymphoid tissue
MDA	Malondialdehyde

MDSC	Myeloid-derived suppressor cells
miRNA	MicroRNA
NDK	Nucleoside diphosphate kinase
NF-κβ	Nuclear factor κ light-chain enhancer of activated B cells
NK	Natural killer
NLRX1	NOD-like receptor family member X1
NO	Nitric oxide
NOX	NADPH oxidase
Nrf2	Nuclear factor erythroid 2-related factor 2
OSCC	Oral squamous cell carcinoma
PBMC	Peripheral blood mononuclear cells
PfEMP1	*P. falciparum* erythrocyte membrane protein 1
PGN	Peptidoglycan
PI3K/Akt	Phosphatidylinositol 3-kinase/protein kinase B
PKC	Protein kinase C
pro-MMP-9	Pro-matrix metalloproteinase-9
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
RNI	Reactive nitrogen intermediates
RNS	Reactive nitrogen species
ROI	Reactive oxygen intermediate
ROS	Reactive oxygen species
SabA	Sialic acid–binding adhesin
SCFA	Short-chain fatty acid
SE	Staphylococcal enterotoxin
Sir2	Silent information regulator 2
SMO	Spermine oxidase
SNP	Single-nucleotide polymorphism
SOD2	Superoxide dismutase 2
T4SS	Type IV secretion systems
TER	Transepithelial resistance
TGF-β	Tumor growth factor β
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α
UC	Ulcerative colitis
VacA	Vacuolating cytotoxin A
WHO	World Health Organization
Wnt	Wingless-related integration site
ZO	Zonula occludens

Introduction

Cancer is a cumulative name of a group of diseases that can start with an uncontrollable abnormal type of cell growth in almost any organ or tissue of the body. Later, the cells metastasize to invade adjoining parts of the body and/or spread to various

organs, being the major cause of death from cancer. According to WHO (www.who.int/health-topics/cancer), cancer is the second leading cause of death in the world with an estimated 9.6 million deaths. Cancer develops in three subsequent stages, namely, initiation, promotion, and progression. In the initiation stage, genotoxic carcinogen or exposure to irritation or inflammation induces an irreversible DNA mutation. In the promotion stage, proneoplastic cells undergo stimulated expansion of clonal growth, and in the progression stage, a clone of an early neoplastic cell is transformed into a fully malignant type, resulting in uncontrolled growth. In bacteria and protozoa-induced cancers, the presence of pathogens or their secreted products induces chronic inflammation and oxidative stress and thus modifies the cellular pathways of the host. To eliminate the pathogen, free radicals are produced by the inflammatory cells including macrophages and eosinophils. These free radicals can oxidize and damage DNA and may initiate DNA mutation in host cells leading to malignant transformation. The pathogenic organisms produce and secrete virulence factors like bacterial toxins, which disrupt and manipulate the homeostasis of host cells affecting cytoskeleton organization, trafficking of vesicles, intracellular signaling pathways, and protein synthesis. The bacterial defensive factors show adverse effects such as DNA damage, genomic instability, resistance to cell death, and signaling pathway alterations. These may cumulatively lead to carcinogenesis (Candela et al. 2014).

Several types of cancers can be induced by pathogenic microorganisms such as *Helicobacter pylori* in gastric cancer and MALT lymphomas, *Chlamydia trachomatis* in cervical cancer, *Salmonella typhi* in gallbladder cancer, and *Fusobacterium nucleatum* and *Bacteroides fragilis* in colon cancer (Kostic et al. 2012). Normal oral microflora maintains homeostatic condition in the oral cavity, but dysbiosis in the oral cavity may favor the growth of acidogenic and aciduric species, namely, Streptococci, Lactobacilli, and Bifidobacteria (Takahashi and Nyvad 2011), to cause dental caries. The growth of *Tannerella forsythia*, *Porphyromonas gingivalis*, *Treponema denticola*, oral Synergistetes, and Saccharibacteria (TM7) has also been found to be responsible for periodontal infections (Al-hebshi et al. 2015). In several studies, periodontitis, being the long-term chronic inflammation of gums, is associated with oral squamous cell carcinoma (OSCC). *Porphyromonas* spp. and *Fusobacterium* spp. are significantly higher in OSCC tissue compared to the healthy mucosa. *P. gingivalis* is associated with pancreatic cancer and gingival squamous carcinoma. *F. nucleatum* is associated with colorectal cancer (CRC) (Kostic et al. 2012).

Chronic inflammatory diseases increase the risk of carcinogenesis in digestive organs, such as inflammatory bowel disease (IBD) for colitic cancer, chronic atrophic gastritis for gastric cancer, chronic hepatitis for hepatocellular carcinoma (HCC) and cholangiocellular carcinoma, and chronic pancreatitis for pancreatic cancer. Inflammation can produce reactive oxygen species (ROS) via neutrophils, macrophage activation, peroxisomes, microsomes, and activation of the mitochondrial energy metabolism pathway. Endogenous production of ROS comes from the mitochondrial respiratory pathway and the NOX enzyme pathway (Block and Gorin 2012). Chronic exposure to high levels of ROS induces tissue remodeling, changes

in gene expression, and DNA damage, resulting in the production of 8-oxo-dG. Lipid peroxidation produces 4-HNE and MDA that can induce angiogenesis. This may activate Wnt/β-catenin and PI3K/Akt signaling pathway and inactivate the tumor suppressor gene PTEN in a time and concentration-dependent manner (Lee et al. 2015). Treatment of cancer patients by using chemotherapy and radiation therapy is a painful process. Moreover, it exerts tremendous physical, emotional, and financial strains on individuals, families, communities, and health systems. In this context, the recent data on probiotic research using cancer cell lines and animal models strongly support its unprecedented ability in cancer prevention and improvement from early stages of cancer. The host having an adequate amount of live probiotic microorganisms gets additional beneficial effects. Many species and strains of *Lactobacillus*, *Lactococcus*, *Pediococcus*, *Enterococcus*, *Streptococcus*, *Leuconostoc*, *Bacillus*, *Escherichia coli*, *Bifidobacterium*, and *Saccharomyces* are predominantly used as probiotics (Fijan 2014). They can protect the intestinal mucosal barrier from toxic substances and pathogens. Therefore, it is able to modulate the immune system and prevent oxidative stress. Probiotic microorganisms create a physiologically restrictive environment by reducing intestinal pH through producing organic acids – lactic acid, acetic acid, bacteriocins, and defensins. These can prevent the colonization of pathogenic bacteria in the gut flora (Ng et al. 2009).

Bacteria-Induced Oxidative Stress Promotes Cancer Development

Oxidative DNA damage is regarded as one of the etiological factors in cancer promotion and progression. Bacterial infections play an important role in carcinogenesis through secretion of pro-inflammatory cytokines and ROS generation. Bacterial infections may also act as a cofactor in metastasis of cancer. In this context, few mechanisms of pathogen-induced carcinogenesis in different physiological systems of humans are discussed below.

Oxidative Stress in the Digestive System

Oral Carcinogenesis

P. gingivalis regulates intrinsic mitochondrial apoptosis pathways by JAK1/STAT3 and PI3K/Akt signaling. The suppression of proapoptotic BAD activity elevates BCL-2 (antiapoptotic): BAX (proapoptotic) ratio that decreases the release of the apoptosis effector cytochrome c. In another different mechanism, *P. gingivalis* inhibits apoptosis through a cascade of events that begins with the upregulation of miRNA-203 in gingival epithelial cells (GECs). Furthermore, nucleoside diphosphate kinase (NDK) secreted by *P. gingivalis* prohibits ATP-dependent apoptosis in GECs. It also interferes with an anticancer immune response mediated by ATP activation of P2X7 receptors on dendritic cells. The activation of IL6/STAT3 by chronic coinfection with *P. gingivalis* and *F. nucleatum* increases the advancement of chemically caused oral cancer (Binder Gallimidi et al. 2015).

FimA adhesion protein of *P. gingivalis* accelerates the cell cycle progression in S and G_2 phases by upregulating cyclins, activating cyclin-dependent kinases (CDKs) by phosphorylation, and decreasing the level of p53 tumor suppressor protein (Pan et al. 2014). The lipopolysaccharide (LPS) of *P. gingivalis* is responsible for dysregulation of p53. *P. gingivalis* may promote GEC proliferation by activating β-catenin via gingipain-dependent proteolysis (Zhou et al. 2015). *P. gingivalis* and *F. nucleatum* has been reported to promote cellular invasion in OSCC. *P. gingivalis* infection activates the ERK1/2-ETS1, p38/HSP27, and PAR/NF-κβ pathways and upregulates pro-MMP-9 expression. Gingipains convert the proenzyme pro-MMP-9 into active MMP-9, which enhances cellular invasion (Inaba et al. 2015). Repeated exposure to *P. gingivalis* can also increase the invasiveness of OSCC cells by inducing epithelial to mesenchymal transition, stemness, and increased production of MMP-1 and MMP-10 (Ha et al. 2015). Infection of human epithelial cells by *F. nucleatum* enhances MMP-13 (collagenase 3) synthesis through activation of mitogen-activated protein kinase p38 and boosts cellular motility, reportedly through stimulation of Etk/BMX, S6 kinase p70, and RhoA kinase (Uitto et al. 2005).

Persistence of infection for a long time generates chronic inflammation, which gradually promotes different stages of carcinogenesis including induction, progression, invasion, and metastasis. ROS, reactive nitrogen intermediates (RNI), and cytokines produced by inflammatory cells contribute to the initiation of cancer by inducing mutations, genomic instability, and epigenetic alterations. Inflammatory cytokines then activate key transcription factors such as STAT3 and NF-κβ within the premalignant cells. This in turn supports the pro-malignant processes including proliferation, angiogenesis, invasion, and metastasis that may later result in a suitable tumor microenvironment (Landskron et al. 2014).

Acetaldehyde, hydroxyethyl radicals, and hydroxyl radicals are carcinogenic metabolites that are capable of forming DNA adducts. The ADH enzyme in certain oral bacteria such as *Streptococcus salivarius*, *S. intermedius*, *S. mitis* (Kurkivuori et al. 2007), nonpathogenic *Neisseria* spp., and *Candida* spp. catalyzes acetaldehyde production at mutagenic amounts under aerobic or microaerophilic conditions.

Oxidative Stress in the Gastrointestinal Tract

Clinical case studies, in vivo experiments in mice, and in vitro assays demonstrate positive correlation between microbe-induced chronic inflammatory disease and progression of carcinogenesis (Takaki and Yamamoto 2015). Colonization of *H. pylori* induces oxidative stress in the infected gastric mucosa and develops chronic atrophic gastritis and gastric cancer.

CagA protein of *H. pylori* induces oxidative stress that leads to chronic inflammation and carcinogenesis. CagA is delivered into gastric epithelial cells via T4SS, after which the pathophysiological actions take place in mitochondria where CagA suppresses tumor suppressor sirtuins (SIRT3). Subsequently, ROS and the hypoxia-related transcription factor HIF-1α get increased. Hypoxia and HIF-1α control a putative HRE positioned at the promoter of a carcinogenesis-related protein AQP3. The ROS-HIF-1α-AQP3-ROS loop not only causes DNA

damage but also prevents DNA repair mechanisms, subsequently causing increased apoptosis. In addition, *H. pylori* infection induces the production of pro-inflammatory cytokines, such as IL-6, IL-8, and TNF, depending on the level of AQP3. CagA protein upregulates Wnt/β-catenin signaling and induces the proliferation of cancer stem cells (Yong et al. 2016).

Oxidative Stress in the Colon

Oxidative stress is an important progenitor and is related to genetic and epigenetic changes in the development of CRC. IBD including Crohn's disease and ulcerative colitis (UC) is a risk factor for colitis-associated CRC. An individual's environment might play an important role in inducing oxidative stress, as the gastrointestinal (GI) tract is constantly exposed to ingested materials and pathogens, including bacteria (Bhattacharyya et al. 2014). ROS-induced oxidized DNA such as 8-OHdG in CpG dinucleotide prevents carcinogenesis-related genes from being methylated. The accumulation of epigenetic alterations in the colon epithelium, such as DNA methylation of tumor suppressor genes, contributes to the development of cancer. IBD is a typical chronic inflammatory disease of the GI tract. Inflammatory cells, such as lymphocytes and neutrophils, are known to infiltrate the active mucosal lesions of UC patients. These cells can even induce active mucosal lesions. Single-nucleotide polymorphisms (SNPs) in the antioxidant gene GPX1 have been linked to UC, and SOD2 is linked to Crohn's disease (CD). This implies that these diseases are genetically linked to oxidative stress (Costa Pereira et al. 2017). Analysis of mitochondrial DNA mutations has revealed that they are prevalent in UC and colon cancer tissue. The higher level of oxidative stress-related 8-OHdG in UC colon tissue indicates that mitochondrial DNA accumulation and oxidative stress are powerful contributors of carcinogenesis.

Streptococcus bovis is a normal gastrointestinal bacterium of ruminants. It increases the expression of some proliferative markers and induces IL-8 production in normal colonic mucosa. Antigens of *S. bovis* are capable of adhering to GI-epithelial, endothelial blood cells as well as to extracellular matrix and can induce IL-8 synthesis. This cytokine promotes oxidative/nitrosative stress and overexpression of COX-2. COX-2 induces cell proliferation mediated by prostaglandin synthesis and local immunosuppression. The synergistic effect of COX-2 is observed with other enzymes, which may promote CRC. In addition, *S. bovis* can induce MMP-2 and MMP-9 and form carcinogenic nitroso compounds that play a crucial role in CRC growth and progression (Tjalsma et al. 2012).

Oxidative Stress in the Reproductive System

Cervical cancer is the fourth most frequent cancer in women as reported in 2018 (WHO). Although the oncogenic human papillomavirus is known to be the major

causative agent, recent reports suggest that *Chlamydia* is also responsible for cervical cancer. The infection with *C. trachomatis* induces ROS production via NOX and NLRX1 pathways (Abdul-Sater et al. 2010) leading to oxidative damage. Intracellular *Chlamydia* first induces NOX-dependent production of ROS, gets diffused into the mitochondrial matrix, interacts with NLRX1, and starts another round of ROS production. *C. trachomatis* can disrupt DNA damage responses (DDR) through alteration of histone modifications and activation of repair inhibitory mechanisms. The organism is also capable of downregulating polymerase beta through miR-499a upregulation, therefore impairing the BER (base excision repair) pathway (Gulve et al. 2019) and leading to single-strand and double-strand breakages in DNA. BER deficiency promotes genetic instability and is closely associated with the development of precancerous conditions. Downregulation of the tumor suppressor protein p53 prevents *Chlamydia*-infected cells from undergoing apoptosis. *C. trachomatis* causes telomere shortening (Prusty et al. 2013), which in turn helps to acquire tumorigenic properties.

Prostatic tissue invasion and intracellular deposition of *Propionibacterium acne* in the glandular epithelial cell are considered to be concomitantly involved in benign prostate hyperplasia and prostate cancer. Prostatic inflammation can be caused by *Propionibacterium acne*, as *P. acne* is the most frequent among all other bacteria that have been isolated from patients with prostate cancer (Davidsson et al. 2016). Oxidative free radicals caused by inflammation are one of those multiple factors that can initiate prostate cancer.

Oxidative Stress in the Respiratory System

Human lungs are exposed to the external environment and contain a specific pattern of microbiota. Among various environmental risk factors, microbes play an important part in maintaining microecological balance in the human lungs. There are certain microbial species in the lung tissues that are involved in regulating the pathogenesis of lung microenvironment. *Chlamydia pneumoniae*, a Gram-negative respiratory pathogen, is a common cause of chronic lung infection and prolonged inflammation (Khan et al. 2016). Epidemiological evidences have shown that *C. pneumoniae* is likely to be related to the growth and development of lung cell carcinoma. ROS generated during inflammation contributes to DNA damage and promotes carcinogenesis. Significant increase of *C. pneumoniae* IgA antibody is considered as a risk factor of adenocarcinoma and small cell carcinoma of the lungs. Chlamydial heat shock protein-60 (CHSP-60) antibodies are thus used as serological markers of prospective lung cancer (Chaturvedi et al. 2010). Healthy individuals' alveolar macrophages emit TNF-α, IL-1, IL-8, as well as superoxide oxygen radicals that have been proven to cause lung tissue and DNA damage. *C. pneumoniae* acts as an effective inducer of TNF-α, IL-1, and IL-6 in host monocytic cells, playing a significant a role in carcinogenesis.

Bacterial Toxins Induced Cancer Development

Manipulation of host inflammatory response is emerging as an important mechanism for bacteria-induced cancer. Bacterial toxins modulate the host's immune system in different manners such as specific immune cell activation and production of cytokines and metabolites to trigger a continuous inflammatory state that subsequently drives cells toward cancer development. Several factors are described below.

DNA-Damaging Toxins

After successful colonization in the GI tract, pathogenic microorganisms secrete several bacterial protein toxins that damage DNA, resulting in DNA mutation, oncogene activation, and cancer development.

Colibactin

The genome of some *E. coli* strains from the phylogenetic group B2 contains polyketide synthase (pks) island that produces the genotoxin colibactin. This colibactin can induce double-strand breaks (DSBs) in DNA of eukaryotic cells (Arthur et al. 2012). This may cause incomplete DNA repair, G_2/M cell cycle arrest, chromosomal instability, and anchorage-independent colony formation. Again, the inflammation of GI tract may induce the growth of microbes, modulate pks island for more colibactin production, and alter the expression of microbial genes that are crucial for tumor development in host cells (Arthur et al. 2012).

Cytolethal Distending Toxin

Gram-negative bacterial pathogens like *Campylobacter jejuni* and *E. coli* strains are reported to produce cytolethal distending toxin (CDT). CDT holotoxin contains three different subunits, namely, CdtA, CdtB, and CdtC. CdtB is responsible for enzymatic activity, while CdtA binds to the host cell membrane. The nuclear transport signal of CdtB N-terminal region helps in nuclear localization and executes its cytotoxicity. In the context of structural and functional aspects, enzymatically active subunit CdtB is homologous to the mammalian DNase I. DNA damage and activation of DDR by CDT intoxication exhibit cytotoxic effects like G_1 and/or G_2 phase arrest and activation of DNA repair mechanisms. The cells that are unable to repair the damage eventually undergo senescence or apoptosis (Guerra et al. 2011). Frequent exposure to DNA damaging agents of endogenous (ROS) and exogenous (ionizing radiation) sources stimulates tumor initiation by altering gene expression of key proteins involved in DDR, cell cycle regulation, or DNA repair pathways. Prolong exposure of sublethal doses of CDT increases frequency of mutations, chromosomal aberrations, and impairment of the DDR. The B subunit of CDT is also present in typhoid toxin produced by *Salmonella enterica* serovar Typhi. CdtB-encoding *Salmonella* induces cell cycle arrest in the G_2/M phase (Rodriguez-Rivera et al. 2015).

Cell-Signaling-Disrupting Toxins

Bacterial protein toxins can act on immune cells through interfering with cell proliferation pathways. These deregulated inflammatory responses further stimulate cells towards cancer progression. Some of the cell signal disrupting toxins and their roles in promoting carcinogenesis are described below.

Cytotoxin-Associated Gene A (CagA) and Vacuolating Cytotoxin A (VacA)

Helicobacter pylori is a microaerophilic Gram-negative bacterium that selectively colonizes in the acid-rich gastric epithelium and gastric mucosa of the human stomach (Moodley et al. 2012). *H. pylori* is classified as class I carcinogen by the International Agency for Research on Cancer (IARC), as it is responsible for several gastric diseases such as chronic gastritis and ulceration to neoplastic changes in stomach tissues (Cid et al. 2013). A complex process involving numerous factors including host genetic susceptibility factors, environmental factors, and the virulence factors of *H. pylori* helps to establish a proper carcinogenic milieu for gastric cancer (Ferreira et al. 2014). In *H. pylori*, these virulence factors are encoded from CagA and SabA gene present in the pathogenicity island, whereas peptidoglycan (PGN) and LPS help in immune evasion for which persistence of infection elicits chronic inflammation-mediated carcinogenesis.

Cytotoxic Necrotizing Factor 1

Some pathogenic *E. coli* strains produce the CNF1 protein toxin that can permanently activates Rho GTPase family proteins. Three groups of GTPases, Rho, Rac, and Cdc42, are activated by CNF1 through the deamidation of a pivotal glutamine residue, glutamine 63 in Rho or 61 in Cdc42. As a master regulator of the actin cytoskeleton, CNF1-activated Rho GTPase generates several actin-dependent events in cells. These include multi-nucleation, nuclear constriction, budding, multipolar metaphases, increase in cellular motility, and activation of NF-κβ via the stimulation of the Akt/Iκβ kinase pathway (Boyer et al. 2004). Apoptosis can be prevented by increasing the number of antiapoptotic proteins and promoting Rho-dependent cell spreading through CNF1.

Bacteroides fragilis Toxin

Bacteroides fragilis is an opportunistic pathogen and present as normal colonic microbiota due to its adherent nature with the mucosal layer in the colon (Dejea et al. 2013). *B. fragilis* toxin (BFT), a metalloprotease protein toxin from ETBF strain, is responsible for its pathogenicity in diarrheal disease, IBD, and CRC. BFT binds to the intestinal epithelial cell receptor, stimulates the cleavage of the tumor suppressor protein E-cadherin, and activates Wnt and NF-κβ signaling pathways (Dai et al. 2019). ETBF can increase tumorigenesis due to boosted STAT3 expression and promotes the recruitment of the highly pro-inflammatory subset of T helper type 17 lymphocytes. The pro-carcinogenic role of BFT is to develop a deregulated inflammatory response.

Staphylococcal Enterotoxins

Staphylococcal enterotoxins (SEs) of *Staphylococcus aureus* stimulate the large population of T cells leading to the production of a cytokine array (Pinchuk et al. 2010). SE may play an influential role in the malignant expansion and the evolution of immune dysregulation in patients with cutaneous T-cell lymphoma (CTCL), and thus, CTCL patients are frequently colonized with *Staphylococcus aureus*. Recent evidences demonstrate that SEs generate crosstalk between benign and malignant T cells causing a STAT3-mediated IL-10 production by the malignant T cells. The SEs subsequently alter the interactions between malignant and benign immune cells, resulting in greater cellular immunity suppression and disease activity in the patient. This leads to further deterioration of the skin barrier (Krejsgaard et al. 2014). The weakened host defense leads to the colonization of *S. aureus* and propagation, and these eventually increase the susceptibility of hosts to secondary infections.

Avirulence Protein A

Salmonella typhimurium is a major cause of human gastroenteritis. Chronic infections are often associated with hepatobiliary cancers. *Salmonella typhi* secreted protein toxin AvrA is associated with hepatobiliary cancers and colon cancer. It modulates inflammation, apoptosis, and proliferation of epithelial cells by changing the ubiquitination and acetylation of target proteins. AvrA enhances colonic tumorigenesis through activation of Wnt/β-catenin signaling pathway (Lu et al. 2014). AvrA plays an important role in several other pathways including oxidative phosphorylation, mTOR, and MAPK (Liu et al. 2010). AvrA-expressing bacteria can activate the STAT3 pathway leading to enhanced proliferation, thereby promoting tumorigenesis (Liu et al. 2010). It has been reported to enhance ROS production and c-Myc expression and thus considered as a key factor promoting CRC (Satuman et al. 2021).

FadA

Fusobacterium nucleatum, a Gram-negative anaerobic normal microflora of the oral cavity, has become one of the most prevalent species found in extraoral sites under diseased conditions (Han 2015). The abundant presence of *F. nucleatum* in CRC patients makes it a potential candidate for CRC susceptibility. In patients with adenomas and adenocarcinomas, *F. nucleatum* levels are ten to 100 times higher than in healthy people, promoting an upsurge in the expression of inflammatory and carcinogenic genes. The FadA adhesion with host E-cadherin generates carcinogenic effect by activating β-catenin signaling and increasing the expression of transcription factors, oncogenes, Wnt genes, and inflammatory genes. These cumulative events stimulate the growth of CRC cells (Rubinstein et al. 2013).

The mechanisms of oxidative stress-induced carcinogenesis by pathogenic bacteria are shown in Fig. 1.

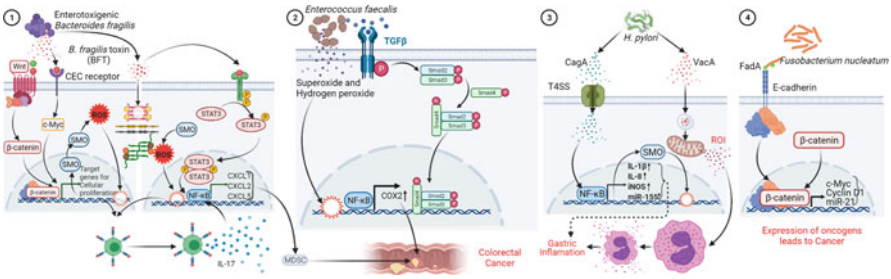

Fig. 1 The mechanism of oxidative stress-induced carcinogenesis by pathogenic bacteria. (1) Enterotoxigenic *Bacteroides fragilis* (ETBF) synthesizes BFT that binds to specific CEC receptor. BFT targets epithelial cell tight junctions, resulting in E-cadherin cleavage and activation of β-catenin that stimulates cellular proliferation through Wnt/β-catenin pathway. Simultaneously, it increases the expression of SMO gene via c-Myc, which in turn promotes SMO-dependent ROS production and DNA damage, increasing the risk of colon carcinogenesis. ETBF up-regulates STAT3 expression. This results in upregulation of IL-17 secretion and thus activates NF-κβ pathway and secretion of some specific chemokines (CXCL1, CXCL2, and CXCL5). This recruits myeloid-derived suppressor cells (MDSCs) and induces carcinogenesis. (2) *Enterococcus faecalis* generates extracellular superoxide and hydrogen peroxide, which further induces NF-κβ signaling through DNA damage and inflammation. *E. faecalis* can also express TGF-β in the intestinal epithelial cells, thereby activating the Smad signaling pathway. The superoxide produced by the microbiota can cause chromosome instability by enhancing the expression of COX-2 through the release of TNF-α from macrophages and thus initiates colorectal cancer. (3) *Helicobacter pylori* expresses a virulent microbial oncoprotein, i.e., CagA, that enters into gastric epithelial cells through T4SS. This induces gastric carcinogenesis through increased SMO level, thereby causing DNA damage. CagA induces NF-κβ pathway, which further increases the expression of cytokines (IL-1β and IL-8) and inducible nitric oxide synthase. A mediator of inflammation, nitric oxide is generated from iNOS. Furthermore, activation of NF-κβ upregulates the expression of miR-155, a microRNA associated with gastric inflammation. Another virulence factor, VacA, induces chemokine expression through Ca^{2+} influx as well as mitochondrial generation of reactive oxygen intermediates (ROIs) from human eosinophils, leading to chronic inflammation of the gastric mucosa. (4) *Fusobacterium nucleatum* invades colorectal epithelium with the help of FadA adhesin, which binds to E-cadherin, thereby activating β-catenin signaling. This increases the expression of oncogenes such as c-Myc and cyclin D1 and microRNA-21. Upon infection with *F. nucleatum*, the production of pro-inflammatory cytokines (IL-6 and IL-8) gets enhanced from immune cells

The Role of Protozoa in Cancer Development

Toxoplasma gondii

Toxoplasma gondii, the causative agent of toxoplasmosis, is found to be associated with various diseases, such as central nervous system neoplasia, meningioma, pituitary adenoma, primary intraocular B-cell lymphoma, nasopharyngeal carcinoma, embryonal carcinoma, gynecological benign tumors, cervical cancer, primary intraocular lymphoma, and primary intraocular B-cell lymphoma. Due to encystation, they can survive in the brain for a long time where elevated

inflammation and inhibition of apoptosis increase the risk of brain cancer. *T. gondii*-infected host cells show resistance to multiple inducers of apoptosis, including Fas-dependent and Fas-independent cytotoxic T lymphocyte (CTL)-mediated cytotoxicity. Over-stimulation of the pituitary gland to fight the parasitic infection may lead to adenoma formation. *Toxoplasma* spp. have been reported to promote brain carcinogenesis through alteration of the host miRNAome (Thirugnanam et al. 2013).

Cryptosporidium parvum

Cryptosporidium parvum, the causative agent of cryptosporidiosis, has been correlated with digestive carcinogenesis, mainly colorectal cancer (Sulzyc-Bielicka et al. 2018). Coproantigens of this parasite can be found in the feces of patients with tumors located in the sigmoid and descending colon. *C. parvum* is found to be associated with cystic hyperplasia of the colonic mucosa, aural-pharyngeal polyps, gastrointestinal neoplastic changes, invasive adenocarcinoma, invasive gastrointestinal and biliary adenocarcinoma, glandular cystic polyps, and intramucosal adenocarcinoma. Altered gene expression of BCL-2, c-Myc, APC, and β-catenin during *C. parvum* infection is potentially involved in the development of *C. parvum*-induced ileocecal oncogenesis and neoplasia (Benamrouz et al. 2014).

Trichomonas vaginalis

Trichomoniasis caused by the protozoan *Trichomonas vaginalis* has become an emerging risk factor of cervical neoplasia and prostate cancer. Virulent isolates of *T. vaginalis* from patients with cervical neoplasia condition show the presence of a large number of hydrogenosomes and vacuoles that can aggravate cervical neoplasia (Yusof and Kumar 2012).

Plasmodium falciparum and Burkitt Lymphoma

In 1982, malaria and Epstein-Barr virus (EBV) were identified as cofactors in the pathogenesis of endemic Burkitt lymphoma. The main risk factor for endemic Burkitt lymphoma is coinfection with *P. falciparum* and EBV. Erythrocytes infected with *P. falciparum* adhere to B cells with the help of the CIDR1α domain of PfEMP1 and induce B cell activation, proliferation, and differentiation into plasma cells (Simone et al. 2011). Increased proliferation of polyclonal B cell population intensifies the risk of expansion and transition of EBV-infected B cells and might be a potential threat to the emergence of a malignant B cell clone. *P. falciparum* inhibits EBV-specific T cell immunity and increases the risk of Burkitt lymphoma through the growth and aberrant proliferation of EBV-infected B cells. *P. falciparum*-induced elevated viral load intensifies the oncogenic effects with the development of

lymphoma. Activation-induced cytidine deaminase (AID) plays a key role in regulating chronic malaria and promoting malaria-induced lymphomagenesis. Malaria is not a direct cause of cancer itself, but *P. falciparum* infection changes the lymphoma phenotype that favors mature B cell lymphomas by encouraging extended AID expression in germinal B cells (Robbiani et al. 2015).

Entamoeba histolytica

Entamoeba histolytica, the causative agent of amoebiasis, adheres to the mucus layer of the intestine followed by colonization and destruction of the host's extracellular matrix. Host immune response against amoebae includes secretion of abundant IgA to prevent pathogens from adhering and penetrating the mucus layer, recognition of the pathogens via Toll-like receptor surrounded by intestinal epithelial cells to activate NF-κβ, and further production of inflammatory cytokines. Neutrophils and macrophages activated by IFN-γ can be attracted to the site of infection and produce ROS and NO to kill the trophozoites. In the chronic stage of infection, the amount of ROS and reactive nitrogen species (RNS) are highly elevated in the microenvironment of the intestinal tract. This increases the oxidative stress in host cells and eventually causes the damage of DNA. *E. histolytica* contains its own defense mechanism to survive against the oxidative stress (Biswas et al. 2021; Dam et al. 2019b). The trophozoites of *E. histolytica* are found to coexist with malignancies, including lung adenocarcinoma, cervical squamous carcinoma, perineal carcinoma, and sigmoid and colonic adenocarcinoma (Varet et al. 2018). Chronic intestinal amoebiasis sometimes manifests into a tumorous, inflammatory mass, called ameboma. Ameboma can be formed in patients with invasive amoebiasis (Jaiswal et al. 2015).

Blastocystis hominis

Blastocystis hominis is an enteric protozoan parasite having a controversial pathogenic potential and reported to be associated with CRC. Stimulation with *Blastocystis* spp. antigen results in increased proliferation of HCT116 cells. Colon cancer cells produce higher levels of IL-6 and IL-8. IL-6 helps in the proliferation of human colon and colorectal carcinoma cells. Peripheral blood mononuclear cells (PBMCs) and HCT116 cells treated with *Blastocystis* spp. antigen show differential patterns of IL-6, IL-8, TNF-α, IFN-γ, proapoptotic p53, and cathepsin B. The *Blastocystis* ST7-produced cysteine protease cathepsin B has been associated with enhanced Caco-2 cell monolayer permeability. Cathepsin B in high concentrations may intensify colon cancer cells by diminishing the cellular immune response. *Blastocystis* spp. isolated from symptomatic patients causes oxidative damage in the animal model, suggesting the role of oxidative stress in developing the pathophysiology of cancer (Kumarasamy et al. 2013).

Giardia lamblia

Giardia lamblia, the causative agent of giardiasis, has been found to coexist with tumor masses in the pancreas and gallbladder in some sporadic cases. In adenocarcinoma, the presence of *Giardia* parasite may be speculated for having a potential relationship between giardiasis and carcinogenesis (Hurnik et al. 2019).

Therapeutic Roles of Probiotics in Cancer Treatment and Prevention

Probiotics play an important and protective role against cancer development. They are now being used as an alternative drug for the treatment of various cancers. This is because they may possess several factors compared to other bacteria. The role of various probiotic strains for the prevention and treatment of cancer is listed in Table 1 and Fig. 2.

Production of Antimicrobial Substances

Inappropriate use of antibiotics has created the worldwide emergence of resistant microorganisms. Nowadays, the biomedical importance of antimicrobial peptides is being explored as novel therapeutics for several diseases. Antimicrobial peptides (AMPs) are the small biologically active molecules, produced by organisms through their innate immune system. Bacteriocins are small AMPs produced by bacteria including probiotics. A few reports have suggested that AMPs including bacteriocins have cytotoxic effects against cancer cells. Probiotic *E. coli* Nissle 1917 induces the mucosal epithelium to produce human β-defensin 2, an AMP having an ability to control adherence and invasion (Schlee et al. 2007). *Lactobacillus brevis* strain 925A produces a bacteriocin, brevicin 925A, which shows an effective role against dental caries and food poisoning pathogens like *Streptococcus mutans* and *Listeria monocytogenes*. *Lactococcus lactis* produces lacticin 3147, a bacteriocin that inhibits *C. difficile*-associated diarrhea. *B. bifidum* NCFB 1454 produces bifidocin B that shows bacteriocin activity against Gram-positive bacteria. *Lactococcus lactis* produces two naturally occurring variants of bacteriocins, Nisin Z and A, having an antitumor potential against head and neck squamous cell carcinoma. Moreover, it shows antimicrobial activity against periodontal pathogens including *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum*, which are responsible for oral cancer (Kamarajan et al. 2020).

Improvement of Intestinal Barrier

Diffusion of potential detrimental factors from the intestinal lumen into the tissue is prevented by the intestinal epithelial junctional complex. Disruption of epithelial junctional complex leads to the loss of mucosal integrity and barrier function that

Table 1 Therapeutic roles of probiotics in cancer prevention and treatment

Sl. no.	Probiotic strain	Cells and host used in the study	Effect	Mechanism of action
1	*Escherichia coli* strain Nissle 1917	HT-29 cells	Modulation of mucosal immunity	MUC2, MUC3, MUC5A, and MUC5AC ↑ (at both gene and protein levels)
2	*Lactobacillus plantarum* 299v	HT-29 cells	Modulation of mucosal immunity	MUC2 and MUC3 ↑ (at gene level); adhesion of enteropathogenic *E. coli* ↓
3	*Saccharomyces boulardii*	BALB/c mice	Enhancement of intestinal mucosal immunity	SIgA production ↑; IgA antitoxin A production ↑
4	*Pediococcus acidilactici* K15	20–64 year-old persons	Enhancement of intestinal mucosal immunity	SIgA production ↑
5	*Lactobacillus rhamnosus* GG	NA	Inhibition of pathogenic microorganisms	Production of lactic acid ↑; growth of *Salmonella typhimurium* ⊥
6	*Bifidobacterium breve* strain Yakult, *Bifidobacterium pseudocatenulatum* DSM 20439	Male BALB/c mice	Inhibition of pathogenic microorganisms	Production of acetic acid ↑; Stx (toxin) production by *E. coli* O157:H ⊥
7	*Lactococcus lactis* MG1363 (pOMO2) (pMRC01)	Culturable gut flora	Inhibition of pathogenic microorganisms	Production of lacticin 3147 ↑; *C. difficile* ⊥
8	*Bifidobacterium bifidum* NCFB 1454	NA	Inhibition of pathogenic microorganisms	Production of bifidocin ↑; *Listeria*, *Bacillus*, *Enterococcus*, *Leuconostoc*, etc. ⊥
9	*Lactobacillus rhamnosus* GG	Caco-2 cells	Prevent the disruption of intestinal barrier by H_2O_2	Activation of ERK1/2, PKCβ1, and PKCε; redistributions of occludin, ZO-1, E-cadherin, and β-catenin ⊥; disruption of transepithelial resistance ⊥
10	*Bifidobacterium bifidum* OLB6378	Neonatal Sprague-Dawley rats	Improvement of intestinal integrity	Neonatal necrotizing enterocolitis ↓; IL-6, mucin-3, and trefoil factor 3 level

(continued)

Table 1 (continued)

Sl. no.	Probiotic strain	Cells and host used in the study	Effect	Mechanism of action
				↑; improves expression of adherens and tight junction proteins
11	*Lactobacillus fructosus* C2	Caco-2 cells	Prevention of intestinal epithelial barrier integrity damaged by enterotoxigenic *E. coli* strain K88 and *S. typhimurium* SL1344	Permeability of dextran ↓; IL-8 ↓; phosphorylation of ERK and JNK ↓
12	*Lactobacillus rhamnosus* GG	HT-29 and T84 cells	Anti-inflammatory role of natural commensal-origin DNA	IL-8 ↓; IκBα degradation ↓; p38 phosphorylation ↓; TER ↑↑
13	*Lactobacillus suntoryeus* HY7801	Male ICR mice	Reduction in expression of pro-inflammatory cytokines	NF-κβ and TLR-4↓; IL-1β and IL-6 ↓; TNF-α ↓; β-glucuronidase ↓
14	*Lactobacillus kefir* IM002, *Bifidobacterium adolescentis* FRP 61, *Bifidobacterium longum* FRP 68 and FRP 69, *Bifidobacterium breve* FRP 334, and *Leuconostoc mesenteroides* IM080	HT-29 cells	Attenuation of *Salmonella enterica* serovar *Typhimurium* DT104 induced inflammation	IL-8 ↓
15	*Lactobacillus fermentum* E-3 *and Lactobacillus fermentum* E-18	NA	Prevention of oxidative stress by producing antioxidative enzymes	Mn-SOD ↑; Glutathione ↑
16	*Lactobacillus casei* BL23	Female BALB/c mice	Prevention of oxidative stress by producing antioxidative enzymes	Body weight ↑; intestinal inflammation ↓; SOD and catalase ↑; level of IFN-γ and IL-10 ↑
17	*Lactococcus lactis*	BALB/c mice	Prevention of oxidative stress by producing antioxidative enzymes	Level of catalase ↑; Damages and inflammation of intestine ↓

(continued)

Table 1 (continued)

Sl. no.	Probiotic strain	Cells and host used in the study	Effect	Mechanism of action
18	*Clostridium butyricum* MIYAIRI 588	344 male Fischer rats	Prevention of oxidative stress by butyrate production	Endotoxin levels ↓; NF-κβ ↓; hepatic TNF-α production ↓; activation of AMPK and AKT Nrf2 ↑; liver steatosis and insulin resistance ↓; prevention of hepatic carcinogenesis ZO-1 and occludin ↑
19	*Lactobacillus helveticus* CD6	NA	Antioxidative role of folate-producing probiotic bacteria	Level of folate ↑; reduces oxidative stress ↑; antimicrobial activity against pathogen ↑
20	*Bacillus* sp. strain LBP32	RAW264.7 macrophage cells and ICR mice	Extracellular polysaccharides secreted by probiotic bacteria possess antioxidant activity	Nitric oxide and nitric oxide synthase ⊥; IL-6, NF-κβ, and TNF-α ↓; activation of p38 MAPK and c-Jun N-terminal kinase; survival rate of mice ↑
21	VSL#3, a probiotic mixture that contains *Streptococcus salivarius* subsp. *thermophilus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium breve*	Young adult mouse colon cells	Probiotics ameliorate the activation of transcription factor mediated by ROS	NFκB ↓; HSP ↑
22	*Lactobacillus* GG	Young adult mouse colon cells	Protection from oxidative stress by activating MAP kinases	Hsp25 and Hsp72 ↑; activate MAPKs (ERK1/2, p38, and JNK)

(continued)

Table 1 (continued)

Sl. no.	Probiotic strain	Cells and host used in the study	Effect	Mechanism of action
23	*Lactobacillus rhamnosus* and *Lactobacillus acidophilus*	Mongolian gerbils	Reduction of ROS by downregulating cyclooxygenase (COX)	*H. pylori*-induced gastric infection ↓; COX-2 protein expression ↓
24	*Lactobacillus fermentum* CECT5716 (LC40) or *Lactobacillus coryniformis* CECT5711 (K8) plus *Lactobacillus gasseri* CECT5714 (LC9)	Male SHR and Wistar Kyoto rats	Attenuation of vascular ROS levels by reducing the activity of NOX	Body weight ↑; NOX activity ↓; TLR-4 expression ↓; modulation of gut microbiota
25	*Bifidobacterium longum*	HEK293T cells	Antioxidative role due to the expression of Sir2	Deacetylation of SigH and FOXO3a ↑; Mn-SOD and catalase ↑
26	*Lactobacillus casei*	Male Wistar rat	Prevention of oxidative stress	CYPlA1 (jejunum, colon, distal jejunum, ileum, and cecum) ↓; CYP2E1 (cecum) and CYP3A9 (duodenum) ↓
27	*Lactococcus lactis* ssp. *lactis*	SNU-1 human stomach cancer cells	Prevention of stomach cancer via downregulation of antiapoptotic proteins	Cell cycle arrest at G_0/G_1 phase; p53 and p21 ↑; cyclin D1 and retinoblastoma phosphorylation ↓; caspase-3 ↑; Bcl-2 ↓; apoptosis ↑
28	*Lactobacillus pentosus* B281 and *Lactobacillus plantarum* B282	Caco-2 and HT29 human colon cancer cell lines	Attenuation of colon cancer by downregulating cyclin	Cell cycle arrest at G- phase; cyclin A, B1, B2, and E ↓
29	*Bacillus polyfermenticus*	HT-29 and Caco-2 human colon cancer cells	Anticancer activity on different colon cancer cell lines by reducing expression of transcriptional factors	ErbB2 and ErbB3 ↓; cyclin D1 ↓; E2F-1 ↓; tumor size ↓
30	*Lactococcus lactis* subsp. *lactis* 44Lac	HT29 (colon cancer), HeLa (cervical cancer), AGS	Probiotics exert cytotoxic effect on different human cancer cell lines	Cell proliferation ↓; apoptosis ↑

(continued)

Table 1 (continued)

Sl. no.	Probiotic strain	Cells and host used in the study	Effect	Mechanism of action
		(gastric cancer), and MCF-7 (breast cancer)		
31	*Lactobacillus casei* ATCC 334	Human colon cancer cells (SW620) and male BALB/c nude mice	Anti-tumorigenic effect by producing ferrichrome	Apoptosis through JNK signaling pathway ↑
32	*Lactobacillus plantarum* BF-LP284	Female BALB/c mice	Cytotoxic and immunomodulatory role of probiotics	TNF-α and IFN-γ ↑; CD3+ T cell ratio ↑; tumor growth ↓
33	*Lactobacillus casei* CRL 431	Female BALB/c mice	Cytotoxic and immunomodulatory role of probiotics	Tumor growth ↓; CD4+ and CD8+ lymphocyte ↑
34	*Bifidobacterium longum*	Male nude mice and BALB/c mice	Cytotoxic and immunomodulatory role of probiotics	Tumor growth ↓; activity of NK cells and T cells ↑; activity of IL-2 and TNF-α ↑
35	*Bifidobacterium lactis* Bl-04 and *Lactobacillus acidophilus* NCFM	Human	Reduction of carcinogenesis by modulating gut microbiota	Butyrate-producing bacteria (*Faecalibacterium* and Clostridiales spp.) ↑; CRC-associated microbes (*Fusobacterium* and *Peptostreptococcus*) ↓
36	*Bifidobacterium lactis*	Sprague-Dawley rats	Synbiotic treatment against CRC	Colonic neoplasms↓; concentration of short-chain fatty acids ↑; cell proliferation ↓
37	*Butyrivibrio fibrisolvens* MDT-1	Male Jcl:ICR mice	Prevention of CRC by producing butyrate	Rate of butyrate production ↑; modulation of gut microbiota ↑; numbers of natural killer cells ↑; numbers of aberrant crypts ↓
38	*Enterococcus faecium* M74 and *Enterococcus faecium* EF031	NA	Detoxification of mycotoxins	Aflatoxin B1 ↓; patulin ↓
39	*Lactococcus lactis* subsp. *lactis* BY21, *Lactobacillus*	Caco-2 cell lines	Detoxification of mycotoxins	Fumonisin B1 ↓; Fumonisin B2 ↓;

(continued)

Table 1 (continued)

Sl. no.	Probiotic strain	Cells and host used in the study	Effect	Mechanism of action
	plantarum B7, *Lactobacillus pentosus* X8, and *Bacillus subtilis* 168			Caco-2 cells death rate ↓
40	*Bifidobacterium longum* SPM1207	Male Sprague-Dawley rats	Inhibition of harmful enzyme activity	Serum cholesterol level ↓; activity of tryptophanase, urease, β-glucosidase, and β-glucuronidase ↓
41	*Lactobacillus acidophilus*	Human	Inhibition of harmful enzyme activity	Activity of β-glucuronidase, azoreductase, and nitroreductase ↓
42	*Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*	BALB/c mice	Inhibition of harmful enzyme activity	Activity of β-glucuronidase and nitroreductase ↓
43	*Lactobacillus casei* 0908, *Lactobacillus paracasei* 0919, and *Lactobacillus casei* 0900	Caco-2 cells for assessing genotoxicity	Inhibition of harmful enzyme activity	Activity of β-glucosidase and β-glucuronidase ↓; genotoxicity of fecal water ↓
44	*Lactobacillus plantarum* MBTU-HK1	Male Balb/c mice	Inhibition of harmful enzyme activity	Antioxidant activity ↑; TNF-α levels ↓; activity of β-glucosidase and β-glucuronidase ↓

NA, not applicable; ↑, increase; ↓, decrease; and ⊥, inhibition

eventually increases the permeability to allergens, pathogens, and toxic substances (Rao and Samak 2013). Some of the proteins such as scaffold protein (ZO) and transmembrane proteins (occludin and claudin) are localized and involved in the formation of tight junctions. Probiotic *L. rhamnosus* GG prevents changes in occludin, ZO-1, E-cadherin, and β-catenin due to oxidative stress by the activation of ERK1/2 (a subfamily of MAPK) and PKC isoforms PKCβ1 and PKCε. *Bifidobacterium bifidum* OLB6378 exerts protective effects against necrotizing enterocolitis injury by lowering the inflammation in the ileum and improving intestinal integrity. *Lactobacillus fructosus* C2 can exert a therapeutic effect against enterotoxigenic *E. coli* or *S. typhimurium* infection (Yu et al. 2015). Butyrate-producing probiotic *Clostridium butyricum* MIYAIRI 588 improves the expression of tight junction proteins and reduces inflammatory indexes and serum endotoxin levels (Endo et al. 2013).

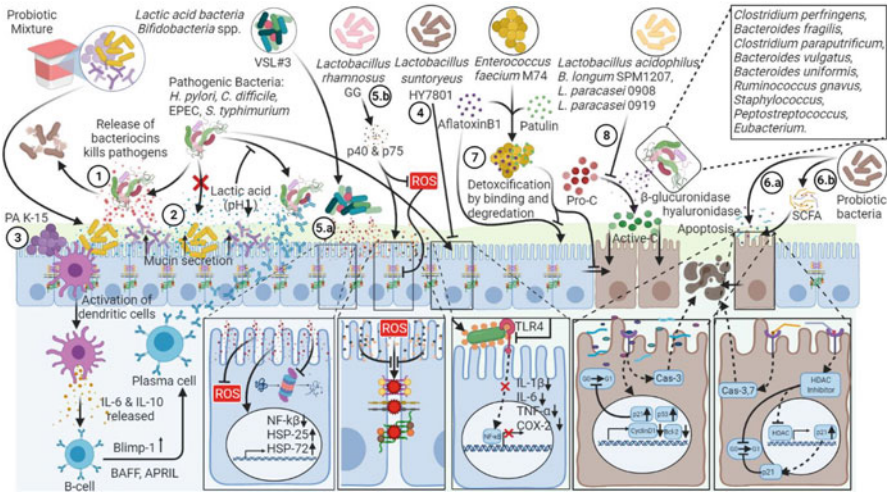

Fig. 2 Role of probiotics in the prevention of cancer. (1) Probiotic microorganisms produce antimicrobial substances such as bacteriocins that inhibit the growth of various pathogens. They also produce some organic acids that lower intestinal pH, thereby preventing pathogenic adhesion in the intestinal epithelium. Lacticin 3147, a bacteriocin produced by *Lactococcus lactis*, inhibits *C. difficile*-associated diarrhea. (2) Mucins are the glycoproteins that are the major constituents of the epithelial mucus layer. Several probiotics promote mucous secretion to improve epithelial barrier function. Adhesion of enteropathogenic *E. coli* (EPEC) is inhibited by *L. plantarum* 299v, and this probiotic strain induces mucin secretion. (3) *Pediococcus acidilactici* K15 (PA) plays a role in the production of IgA in PBMCs. The secretion of IgA in the intestinal mucosa is important to improve host defense against pathogens. Blimp-1, BAFF, and APRIL are involved in the innate pathway of IgA production from B cells. LAB contains several kinds of TLR ligands and activates DCs to secrete many kinds of cytokines such as IL-5, IL-6, and IL-10. These cytokines promote the differentiation of plasma cells that are involved in IgA production. (4) *Lactobacillus suntoryeus* HY7801 (LS) inhibits TLR-4 mediated NF-κβ activation. This decreases the expression of pro-inflammatory cytokines such as IL-1β, IL-6, COX-2, and TNF-α. The activity of harmful bacterial enzymes such as β-glucuronidase and hyaluronidase is significantly reduced by HY7801. (5) Antioxidative role of probiotics. (**a**) VSL#3, a probiotic mixture containing *Streptococcus salivarius* subsp. *thermophilus*, *Lactobacillus casei*, *L. plantarum*, *L acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium longum*, *B infantis*, and *B. breve*, produces a soluble factor that inhibits the activity of proteasome after an early exposure of the probiotic-conditioned media. VSL#3 treatment reduces the release of MCP-1 in response to NF-κβ activation by TNF-α. The expression of anti-inflammatory and cytoprotective HSPs such as HSP 25 and HSP 72 is increased, and oxidative stress is reduced in colonic epithelial cells after probiotic treatment. (**b**) *Lactobacillus rhamnosus* GG (LGG) produces soluble proteins p40 and p75 that alleviate H_2O_2-induced disruption of tight junctions and TER. Pretreatment with p40 or p75 blocks the selective inhibitors such as U0126 (MAP kinase inhibitor) and Ro-32-0432 (PKC inhibitor) that results in the activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2, a subfamily of MAPK) and PKC isoforms PKCβ1 and PKCϵ. The activation of ERK1/2 and PKC isoforms protects junction proteins such as ZO-1, occludin, E-cadherin, and β-catenin from oxidative stress-induced redistribution. (6) Antiproliferative and apoptotic role of probiotics and short-chain fatty acids. (**a**) *Lactococcus lactis* ssp. *lactis* (*L. lactis*) exerts antiproliferative effects on the SNU-1 human stomach cancer cells by arresting G_0/G_1 phase, increasing the expression of p53 and p21, and reducing the level of cyclin D1. (**b**) SCFAs such as butyrate and propionate play an important role in the induction of apoptosis. Butyrate increases the expression of p21 and induces HDAC inhibition,

Modulation of the Immune System

Probiotic microorganisms produce molecules with immune-regulatory and anti-inflammatory functions that can modulate the host immune system by stimulating dendritic cells (DCs) and natural killer (NK) cells of the innate immune system. The primary immune response is triggered by different pattern recognition receptors like Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) expressed on various immune cells like DCs, NKs, and non-immune cells such as epithelial cells, endothelial cells, and fibroblast cells (Bermudez-Brito et al. 2012). TNF-α stimulates NF-κβ, which initiates the transcription of a series of genes including IL-8, IL-6, IL-1β, COX-2, and p-65. *Lactobacillus rhamnosus* GG enhances the expression of TLR-9 that attenuates TNF-α-enhanced NF-κβ activity (Ghadimi et al. 2010). *Lactobacillus suntoryeus* HY7801 inhibits TLR-4-linked NF-κβ activation and decreases the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Thus, it can lower the activities of harmful intestinal bacterial enzymes such as β-glucuronidase.

Antioxidant Properties of Probiotics

Oxidative stress can be generated in host cells by various endogenous and exogenous factors. Probiotic microorganisms exert antioxidant activity in different ways such as production of antioxidant enzymes (Fe-SOD and Mn-SOD), secretion of antioxidant metabolites (butyrate and folate), and modulation of molecular signaling pathway (Dam et al. 2019a).

Superoxide, a reactive oxygen species, is abundantly produced by the mitochondria and catalyzed by SOD into hydrogen peroxide and water. *Lactobacillus fermentum* E-3 and E-18, *L. casei* BL23, and *L. lactis* are few examples of probiotic strains that produce antioxidative enzymes such as catalase and SOD that can prevent oxidative stress (LeBlanc et al. 2011).

Probiotic *Clostridium butyricum* MIYAIRI 588 strain produces butyrate that suppresses hepatic oxidative stress, improves oxidative stress-induced damages, and reduces nonalcoholic fatty liver disease (Endo et al. 2013). Probiotic bacteria

Fig. 2 (continued) causing cell cycle arrest at G_1 phase. Propionate induces apoptosis in cancer cells by activating p21 and caspases. (7) Probiotic *Enterococcus faecium* M74 can detoxify the carcinogens, aflatoxin B1 and patulin. (8) β-Glucuronidase and hyaluronidase are the harmful enzymes, produced by intestinal bacteria such as *Clostridium perfringens*, *Bacteroides fragilis*, *Clostridium paraputrificum*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Ruminococcus gnavus*, *Staphylococcus*, *Peptostreptococcus*, and *Eubacterium*. This enzyme produces carcinogenic aglycones by hydrolyzing β-glucuronides. Elevated levels of β-glucuronidase enzyme in plasma increases the risk of developing cancer such as CRC, breast cancer, and prostate cancer. Probiotics, such as *B. longum* SPM1207, *L. paracasei* 0908, *L. paracasei* 0919, and *Lactobacillus acidophilus* can inhibit the activity of harmful bacterial enzymes that can convert pro-carcinogens (ProC) to active carcinogens (ActiveC)

of the genera *Lactobacillus* and *Bifidobacterium* can produce folate, and *Lactobacillus helveticus* can produce 5-methyltetrahydrofolate, a folic acid derivative. The intracellular cell-free extract of *Lactobacillus helveticus* CD6 can scavenge DPPH radical and chelate Fe^{2+} and inhibits the rate of ascorbate autoxidation (Ahire et al. 2013). Folate availability affects the efficiency of DNA methylation and gene expression, whereas folate deficiency leads to DNA hypomethylation that results in overexpression of oncogenes and inactivation of tumor suppressor genes. Even low folate intake may enhance the chance of breast cancer among postmenopausal women (Sellers et al. 2001).

The extracellular polysaccharide secreted from *Bacillus* sp. strain LBP32 prevents inflammation induced by lipopolysaccharide from *Escherichia coli* 0111:B4 in RAW 264.7 cells. It also inhibits the release of pro-inflammatory cytokines, activation of NF-κβ, and ROS production (Diao et al. 2014). Several enzymes (COX, CYP, and NOX) are involved in producing ROS. Mucosal expression of COX-2 is downregulated in *H. pylori*-infected Mongolian gerbils upon the treatment of Lacidofil, a mixture of probiotic *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* (Brzozowski et al. 2006).

Antiproliferative Activity of Probiotics

Uncontrolled cell proliferation if unchecked by apoptosis can lead to cancer progression. Probiotic microorganisms inhibit growth and proliferation of cancerous cells. Probiotic bacteria are the focus of research in recent days because of their anticancer properties. However, they can do it through a combination of versatile processes that includes the suppression of the microbial growth accountable for the production of mutagens and carcinogens, the protection of DNA from oxidative damage, the alteration of carcinogen metabolism, and the regulation of expression of various genes involved in cell death and apoptosis. Short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate are produced from complex carbohydrates by the intestinal microbiota and play an essential role in suppressing carcinogenesis (Adom and Nie 2013). Several probiotic strains modulate the gut microbiota composition by increasing SCFAs producing bacterial count. SCFAs can bind with various G-protein-coupled receptors (GPRs) such as GPR41, GPR43, and GPR109. GPR43 plays an effective role in the induction of apoptosis and regulation of cell proliferation. Propionate exerts an anti-tumor effect in colon cancer cells via GPR43. GPR43/propionate treatment reduces the level of proliferating cell nuclear antigen and enhances apoptotic cell death. GPR43 with propionate acts as an apoptosis inducer and a tumor suppressor in colon cancer (Tang et al. 2011). Application of *B. lactis* significantly enhances the production of SCFA, and that can give protection from the development of CRC (Le Leu et al. 2010). Butyrate effectively regulates cell proliferation by inhibiting histone deacetylase (HDAC), which in turn leads to the overexpression of p21. This eventually leads to the cell cycle arrest at G_1 phase in cancer cells and thus inhibits colon carcinogenesis (Adom and Nie 2013). Probiotic microorganisms reduce the activity of harmful enzymes

β-glucuronidase and β-glucosidase. β-Glucuronidase hydrolyzes β-glucuronides and produces carcinogenic aglycones. The elevated level of β-glucuronidase enzyme in plasma increases the risk of developing colorectal cancer, breast cancer, and prostate cancer (Mroczynska et al. 2013). Probiotic bacteria *B. longum* SPM1207 and *Lactobacillus acidophilus* play an important role in inhibiting the activity of such harmful enzymes (Lee et al. 2009).

Future Perspective

Extensive epidemiological evidences indicate the role of microbes in inducing 20% of all cancers. The use of probiotic bacteria is becoming a promising tool in cancer therapy. The world market for probiotics is growing at an estimated yearly rate of 7%. Although probiotic treatment has emerged as an effective alternative to combat the severity of cancer, lack of clinical and preclinical studies and some unwanted side effects demand caution during its application on humans. It is rarely used in routine clinical practice as there are very few commercially available strains. The exact bioactive component of the probiotics that provides beneficial effects should be addressed in order to step up the basic studies into clinical trials. Although the scenario of probiotics in cancer therapy seems alluring, the advancement is not linear. Safety assessment of probiotics seems to be the biggest issue at this point. Identification of the most beneficial strains for cancer prevention in humans necessitates a large database as a starting point. Novel engineered probiotic microorganisms may offer new insights into therapeutic usage for the prevention and treatment of cancer. More clinical and preclinical studies are needed to gain the most effective outcome from probiotic therapy in regulating a targeted human flora that may aid in the development of personalized medicine in the future.

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