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CHAPTER 8

Correlation Between Reactive Oxygen Species (ROS), Inflammation, and Probiotics

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ABSTRACT

Key signaling molecules called Reactive Oxygen Species (ROS) are crucial in the development of inflammatory diseases. Endothelial dysfunction and tissue damage are brought on by polymorphonuclear neutrophils (PMNs), which increase the production of ROS at the site of inflammation. The body's immunological response is triggered by infections and damage. Free radicals are created by immune cells called macrophages as they combat foreign pathogens. Inflammation can result from the damage these free radicals can do to healthy cells. Probiotic bacteria have the ability to both increase and decrease the production of anti-inflammatory cytokines, which play an important role in the prevention of carcinogenesis. They are also capable of activating phagocytes to eliminate early-stage cancer cells. The use of

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probiotics could improve the gut microbial population, increase mucus secretion, and prevent the destruction of tight junction proteins by decreasing the number of lipopolysaccharides. Additionally, probiotic treatment may lessen the formation of inflammatory biomarkers and reduce unnecessary immune system activation by reducing gut dysbiosis and intestinal permeability. Application of heat-killed probiotic bacteria coupled with radiation had a positive influence on enhancing immunological recognition of inflamed cells. The notion of employing probiotic bacteria as medication delivery vehicles has recently gained traction due to multiple articles revealing promising outcomes. Probiotic bacteria and gut microbiota are anticipated to play a significant role in immunomodulation and the management of inflammation during the next several years. The paper describes how, with the help of thorough literature investigation, the beneficial supplementation of probiotics on oxidative stress enhances antioxidant resistance and increases the quantity of antioxidant enzymes in the human body.

8.1 INTRODUCTION

Probiotic literally means "for life" in Greek. With the growth of interest in taking supplements containing live bacteria, as well as research into the mechanisms of action of these bacteria, we have gained a greater understanding of what a probiotic is. The term was first applied to substances produced by one microorganism that induced the growth of other microorganisms, and it was later applied to tissue extracts that induced microbial growth, as well as to feed additives that had a positive impact on animals by balancing their intestinal flora [1]. It has been shown that probiotics and the fermented metabolites of them have antioxidative properties that control oxidative stress and shield cells from damage caused by oxidants. Inflammation is broadly categorized into acute and chronic, which might be due to various diseases like arthritis, bowel disease, diabetes, cardiovascular diseases, etc. Probiotics show promise as anti-inflammatory agents that may help to treat chronic inflammation and may be used as a preventative measure. One of the most well-researched ways that probiotics may reduce inflammation is through the repair of the mucosal barrier against pathogens. Enhanced intracellular reactive oxygen species (ROS) levels that harm lipids, proteins, and DNA are known as oxidative stress. Oxygen free radicals, prostaglandins, leukotrienes, and nitric oxide are all important mediators of inflammation, including proteins, peptides, glycoproteins, and cytokines. Various cell types, including epithelia, endothelium, and inflammatory cells,

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produce these chemicals [2]. Reactive oxygen species (ROS) are central in the development of inflammatory diseases. Inflammatory sites can be damaged by polymorphonuclear neutrophils that produce ROS and cause endothelial dysfunction. High ROS levels, together with decreased levels of cellular antioxidant enzyme systems, cause malignant transformation via many molecular targets, including NF-κB and nuclear factor (erythroid-derived 2)-like 2 factor (Nrf2). These critical components govern signaling cascades that create an inflammatory milieu that suppresses apoptotic cell death, tumor growth, angiogenesis, and metastasis, all of which contribute to the initiation, development, and progression of malignant neoplasms [2]. Recent research has proven the pivotal role of probiotics in regulating inflammation and the generation of ROS. The current review focuses on the role of probiotics in controlling various inflammatory mediators, including ROS, with the aid of research evidence [2, 1].

8.2 ROS IN INFLAMMATORY DISEASE

A living mammalian tissue's protective response to injury caused by any substance is inflammation, which helps to restore (or replace) damaged tissues as well as localize, get rid of, and remove harmful stimuli. Reactive oxygen species (ROS) are now being demonstrated to play a part in the beginning, progression, and resolution of an allergic response. Moreover, ROS function in intracellular signaling as second messengers and microbicidal agents. Nonetheless, there is convincing evidence that excessive ROS production can cause tissue and cell damage, as well as the chronic inflammation that underlies many neurodegenerative, cardiovascular, and metabolic illnesses. Angiogenesis, respiratory burst, phagocytosis, and increased vascular permeability are all crucial aspects of inflammation, and some of these events also contribute to the resolution of inflammation [3].

In order to initiate signaling cascades that could trigger the emergence and evolution of inflammatory diseases, ROS can either oxidize biomolecules or structurally alter proteins and genes. Inflammation starts when ROS activate transcription factors and genes that promote inflammation. To draw additional immunological cells to the area of contamination or oxidative stress, immunological cells release a variety of chemokines and cytokines during inflammation. Instinctively, immune cells near the site of inflammation produce more ROS, which leads to tissue damage and oxidative stress [4]. Reactive oxygen species, also known as ROS, are free radicals formed via

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molecules or molecular fragments of molecular oxygen, such as hydrogen peroxide (H_2O_2), hydroperoxyl radicals, hypochlorous acid (HOCl), nitric oxide (NO), singlet oxygen ($^1O_2$), and superoxide anion hydroxyl (HO•) [3]. The main source of ROS in various cell types is the cellular mitochondria. The electron transport chain, dehydrogenases in the matrix of mitochondrial cells, the p66^shc^ protein within the space between membranes, and monoamine oxidase in the outer membrane (from complexes of the mitochondrial respiratory chain: complex I—NADH dehydrogenase complex and complex III—cytochrome bc_1 complex) are used to produce reactive oxygen species in this situation. Xanthine oxidase, cyclooxygenases, myeloperoxidase, NADPH oxidase, cytochrome P450 enzymes, lipoxygenases, and oxidoreductase 1 are additional cell enzymes that can produce ROS [5].

DNA, lipids, and proteins are harmed by high quantities of ROS. Yet, ROS function as significant mediators in the control of cell proliferation, adhesion, development, and death. By posttranslational alteration of redox-sensitive proteins, such as different receptors and channels, kinases and phosphatases, caspases, and transcription factors, ROS are implicated in intracellular signaling. Redox-sensitive proteins are those that have functionally important cysteine residues that are susceptible to oxidation. Therefore, sulfhydryl groups of cysteine (Cys-SH) can be oxidized by H_2O_2, leading to the generation of sulfonic (Cys-SO_3H), sulfinic (Cys-SO_2H), and sulfenic (Cys-SOH) acids. Any of these alterations change how proteins behave and impact how they work in the signal transduction pathway [6]. The onset, progression, and resolution of inflammation are all influenced by ROS.

8.2.1 ROS'S ROLE IN CRUCIAL MOMENTS

1. **Leukocyte Extravasation and Vascular Permeability:** When injurious substances activate cells of innate immunity (mostly macrophages and mast cells), they release a variety of inflammatory mediators that enhance vascular permeability and cause leukocyte migration to the site of injury [7].
2. **Phagocytosis and Respiratory Burst:** The most well-known function of ROS in inflammation is their involvement in the respiratory burst phenomenon. At the site of the inflammation, neutrophils and macrophages phagocytize pathogens and cellular debris. This results in the assembly and activation of the NADPH oxidase at

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the phagosome membrane. This enzyme turns O_2 into ROS, which releases additional ROS. ROS produced during respiratory bursts are discharged into the surrounding tissues as well as phagosomes. Most of their actions are bactericidal [8].

3. **Angiogenesis:** Angiogenesis, the act of creating fresh blood vessels, is a critical phase in the proliferative stage of inflammation. There is proof that ROS produced by the oxidase enzyme NADPH are essential for this stage of an inflammatory response. Human umbilical vein endothelial cells (HUVECs) contain NADPH oxidase and have been connected to actin and the protein IQGAP1 in the upper region of migratory cells (Ras GTPase-activating-like protein). When this connection is broken, NADPH oxidase is translocated from the leading edge, which impairs endothelial cells' ability to migrate [9].
4. **Resolution of Inflammation:** ROS are involved in a number of procedures that aid in the healing of inflammation. Massive neutrophil death is one of the major processes that occur before inflammation resolves. Granulocytes and other cells undergo apoptosis through signaling pathways that depend on ROS. A mouse model of antigen-induced arthritis has therefore demonstrated that H_2O_2 causes leukocyte mortality and remission of the response to inflammation [10].
5. **Oxidative Stress:** ROS are crucial regulators in almost all stages of the inflammatory process, but excessive ROS produced by leukocyte mitochondria and NADPH oxidases in mice, which is not countered by antioxidant systems, may cause serious cellular and tissue damage and promote the chronic inflammation that underlies many neurodegenerative, cardiovascular, and metabolic diseases [11].

8.3 ROS IN TUMORIGENESIS

8.3.1 SIGNIFICANCE OF ROS IN TUMORIGENESIS

Cancer intricacy is due to its multifaceted and multifactorial appearance. In recent decades, it has been demonstrated that the disturbance of redox balance is one of the most significant causes underpinning cancer formation, development, and metastasis in human cells. This disproportionality in redox balance has been linked to a rise in free radicals, specifically ROS [12].

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Intracellular oxidative metabolism produces a group of molecules called ROS [13]. Singlet oxygen (primary excited state), superoxide anion (single electron state), hydroxyl radical (three-electron state), and hydrogen peroxide (H_2O_2) are among these compounds. It is essential to note that ROS are crucial signaling molecules and can, at low levels, regulate a variety of biological and physiological processes. It is generally thought that intracellular ROS levels remain stable due to the fact that ROS are powerful oxidants responsible for increasing intracellular damage and oxidation to lipids, DNA, and proteins during oxidative stress events [14].

ROS plays a significant part in signaling, cell proliferation, and revascularization in the tumor microenvironment. The progressive increase in ROS levels can similarly stimulate cancer cell growth, diffusion, and metastasis. On the other hand, the damaged DNA of cancer cells partially causes apoptosis and tumor necrosis when the amount of ROS is excessive [15].

The amount of ROS has varying impacts on genetic roles. While cytostatic ROS levels support biological activities, cytotoxic ROS levels trigger cell death and immunological deregulation. Tumors are promoted by ROS when they reach super-physiological or cytostatic levels while avoiding cell death levels. As previously stated, tumor cells can cause reactive stress [16].

8.3.2 REACTIVE OXYGEN SPECIES -MEDIATED INDUCTION OF OXIDATIVE STRESS

ROS levels in a typical cell are maintained through a variety of detoxification processes controlled by antioxidant enzymes [17]. In regular circumstances, the intracellular antioxidant system, which comprises several enzymatic and non-enzymatic components, balances ROS in cells, hence ensuring cellular homeostasis [18]. However, under illness or pathological conditions, the quantity of ROS rises, depleting antioxidants and eventually leading to a disruption in homeostasis or oxidative stress. As a result, during ROS homeostasis, the cells are well regulated, which helps to preserve redox balance in healthy cells. Ketoglutarate dehydrogenase, monoamine oxidase, mitochondrial p66^Shc^ (pro-apoptotic protein), sirtuins, Nrf2, and forkhead box O3 (FOXO3), in addition to the primary redox cycling reactions, are hypothesized to be the source of ROS. This increased ROS generation or defective protective mechanisms may also result in increased oxidative stress, which can contribute to a variety of health issues. Inflammatory cells like macrophages and neutrophils produce ROS as a result of mitochondrial oxidative phosphorylation, P450 metabolism, and peroxisomes [19].

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8.3.3 ACTIVATION OF ROS BY INFLAMMATION MARKERS

Inflammatory cytokines and chemokines are inflammation-related factors. The levels of these inflammation-related factors play a significant role in regulating cancer growth [20]. These factors either produce an antitumor response or induce malignant transformation during cancer development. ROS has been shown to play a significant role in the link between cancer and chronic inflammation, as it can influence the existence, amounts, and types of inflammation-modulating factors such as AP-1, β-catenin/Wnt (wingless-related integration site), HIF-1 (hypoxia-induced factor-1 alpha), NF-κB, PPAR-gamma, p53, inflammatory cytokines, chemokines, and growth regulators [21]. During the process of inflammation within the tumor microenvironment, ROS is produced by enzymes that generate oxidants, namely, inducible nitric oxide synthase (iNOS), myeloperoxidase (MPO), and xanthine oxidase (XO) [22]. In order to remove and disrupt biological, chemical, and biological potential threats, cyclooxygenase 2 (COX-2) and lipoxygenase (LOX) are used. The oxidative damage to DNA, RNA, proteins, lipids, and mitochondria is due to the generous amount of ROS accumulation. This results in an increased mutation stress signal-transduction error, apoptosis inactivation, and an overwhelming production of extra ROS that triggers inflammation-modulating factors, inflammatory cytokines, and chemokines [14]. Aside from inducing persistent inflammation through ROS-mediated NF-κB activation, active NF-κB is thought to be a crucial factor in the progression of treatment-resistant cancers toward intermittent gamma-irradiation therapy and chemotherapeutic drugs. Tumor-associated chronic inflammation and cancer-development hallmarks may be treated by targeting ROS as a treatment. The proliferative signaling, evasion of development restrainers, metastasis, replication immortality, angiogenesis, and intransigence to cell death are all facilitated by ROS [23].

8.3.4 ROS IN CANCER METASTATIC PROCESSES

In cancer, metastasis is the main cause of morbidity and mortality. It involves the spreading of cancer cells to nearby tissues and distant organs. According to research, tumor metastasis is a complicated and multidimensional event caused by the inherent mutational burden of cancerous cells and bidirectional contact distinguishing cancerous and noncancerous cells [24]. The presence of ROS has been shown to contribute to epithelial-to-mesenchymal transition

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(EMT) in numerous studies. In addition, TGF-β1 regulates uPA (urokinase-type plasminogen activator). The ROS-dependent migration and invasion of cells are facilitated by PFA (plasminogen activator) and MMP-9. Hypoxia-mediated MMPs and cathepsin expression are induced by ROS, increasing tumor migration. ROS triggers Nrf2, which promotes Klf9 (Kruppel-like factor 9), activating ERK1/2 and increasing ROS generation in cancer cells [25]. Inhibiting premalignant development can be accomplished by targeting KLF9 with antioxidants.

8.3.5 ANGIOGENIC AND ROS-PRODUCING CELLS

A tumor's blood vessels form from preexisting ones through the preliminary stages of tumorigenesis. The formation of new blood vessels that aid tumor growth and survival occurs in the process of angiogenesis. Angiogenesis dependent on ROS is initiated by cancer proliferation. Cancer growth triggers ROS-dependent angiogenesis, which raises the metabolic rate and results in high levels of ROS [26]. Angiogenic modulators are secreted in response to the elevated ROS levels within the tumor microenvironment. Growth factors are promoted by both endogenous and exogenous ROS. VEGF and hypoxia-inducible factors are two cytokines and transcription factors that promote tumor growth and progression through ROS-dependent cellular signaling (HIF-1) [18]. Many investigations using cancer cell lines (MCF-7, HepG2, H-1299, and PC-3) have demonstrated that ROS works via the PI3K/Akt signaling cascade, boosting HIF-1 expression and angiogenesis. As a result of downregulating neovascularization in accordance with the body of information demonstrating ROS's angiogenic potential, therapeutic targets with antioxidant properties and targeting consequent communication pathways will be useful in managing and treating patients. Another way to improve the course of the disease is through various redox imbalance restoration techniques. Further investigation into disease-specific ROS may have therapeutic implications for future medication development, given the failure of interventional trials using small antioxidants [27].

8.3.6 ROS IN TUMOR CELL PROLIFERATION

Hydrogen peroxide and superoxide at low levels have a significant impact in assisting cell growth in a broad range of cancer cell types. For instance, intracellular oxidative stress in breast cancer cells increases as a result of the

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transformation of estrogen to the mitochondria. ROS formed by mitochondria govern both cell development and inactivity [28]. This is accomplished by MnSOD activity, which acts as a mitochondrial ROS regulator. Higher superoxide and low hydrogen peroxide levels promote proliferation due to reduced manganese superoxide dismutase (MnSOD) activity; however, improved MnSOD activity causes proliferating cells to enter inactivity due to increased hydrogen peroxide production. Inhibiting the enzyme known as the mitochondrial uniporter prevents ROS formation and declines estrogen-induced cell proliferation in breast cancer cells, indicating a role for mitochondrial ROS in tumor progression. ROS-mediated activation of the Erk1/2 MAPK signaling pathway, along with the transcription factor, promotes estrogen-induced cell growth. CREB is a protein that binds to the cyclic AMP response element (CRE). There is an increase in the mRNA levels of cyclins that are involved in the cell cycle due to reactive oxygen species, such as cyclin B2, cyclin D3, cyclin E1, and cyclin E2 [29]. There has been evidence that MCF-10A cells undergo abnormal multiplication due to a lack of redox regulation of the cell series. There was a major variance between the basal stages of endogenous oxidative stress in pancreatic cancer cell lines and normal cells. Higher ROS levels have been associated with higher proliferating cells. A sustained ectopic production of the extremely potent antioxidant enzyme MnSOD slows pancreatic tumor cell development [15].

ATM (ataxia telangiectasia mutated) is one of the proteins that are triggered by ROS in cell cycle regulation. It is possible to reverse equivalent effects in ATM knockout mice with antioxidant supplementation, whereas patients missing ATM have greater levels of oxidative damage. As a result of altering critical proteins involved in the development of cell cycles, ROS might modulate tumor cell proliferation [30].

Table 8.1 summarizes the progression of cancer caused by ROS and Table 8.2 summarizes the contribution of ROS in cancer cell death.

8.4 INTERLINK BETWEEN ROS AND INFLAMMATION IN CANCER

All stages of carcinogenesis are aided by inflammation, which also increases the risk of developing cancer. A complex network of interacting cells, including stromal fibroblasts, many immune cell types, endothelial cells, and cancer cells that infiltrate the host, makes up the tumor microenvironment (TME) [32]. Because of their high plasticity, within the TME, cells' phenotypic and

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TABLE 8.1 Progression of Cancer Caused by ROS [31]

Influence	Mechanism	Cell line
Induces DNA damage	ROS can damage DNA directly, leading to mutations that can promote cancer growth.	HeLa, MCF-7, A549
Activates oncogenes	ROS can activate oncogenes, which are genes that promote cancer growth.	KRAS, BRAF, MYC
Inhibits tumor suppressor genes	ROS can inhibit tumor suppressor genes, which are genes that help to prevent cancer growth.	TP53, PTEN, BRCA1
Increases cell proliferation	ROS can increase cell proliferation by stimulating the cell cycle.	MCF-7, A549
Induces cell survival	ROS can induce cell survival by inhibiting apoptosis.	HeLa, A549
Promotes angiogenesis	ROS can promote angiogenesis, which is the growth of new blood vessels that supply tumors with nutrients.	HeLa, MCF-7
Increases metastasis	ROS can increase metastasis, which is the spread of cancer cells from the primary tumor to other parts of the body.	HeLa, MCF-7

TABLE 8.2 Contribution of ROS in Cancer Cell Death [15]

Influence	Mechanism	Cell line
Induces apoptosis	ROS can induce apoptosis, which is a type of programmed cell death.	HeLa, MCF-7, A549
Stimulates autophagy	ROS can stimulate autophagy, which is a process of cellular self-digestion.	HeLa, MCF-7, A549
Increases ROS sensitivity	Cancer cells can become more sensitive to ROS, which makes them more likely to die.	HeLa, MCF-7, A549
Inhibits cell survival pathways	ROS can inhibit cell survival pathways, such as the PI3K/AKT pathway.	HeLa, MCF-7, A549
Promotes cell death signaling pathways	ROS can promote cell death signaling pathways, such as the caspase cascade.	HeLa, MCF-7, A549

functional features are continually modifying. Chronic inflammation is a key factor in the growth of tumors by producing a TME that is supportive. Many physiological processes depend on ROS, which can operate as messengers inside cells. When ROS reach supraphysiological levels, they are thought to be powerful DNA-damaging agents. Many malignancies have been discovered to have elevated ROS levels, and these elevated levels have been linked to practically every facet of cancer growth. Chronic inflammation and cancer have long been linked to ROS, according to the theory [33].

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The extracellular matrix and blood vessels are acellular components of the tumor microenvironment (TME), while epithelial cells, fibroblasts, and immune cells are examples of cellular components surrounding the tumor mass. In addition to other roles that contribute to the hallmarks of cancer, cancer cells secrete chemicals that modify the TME and promote the progression of the disease through immune evasion, metastatic niche formation, and neo-angiogenesis, among other mechanisms [34].

8.5 AN OVERVIEW OF CANCER ASSOCIATED CHANGES

One of the most concerning diseases in the world is still cancer. By 2030, there will likely be 13 million cancer-related deaths worldwide, demonstrating the critical need for scientific cancer therapies [33]. A group of cells that grow out of control and ignore the usual laws of cell division is what is referred to as cancer, and these cells are referred to as cancer cells [35]. According to recent studies, the loss of redox equilibrium serves a crucial role in the initiation, growth, and eventual spread of cancer in human cells. Free radicals, which are mostly identified as reactive species of oxygen, are overexpressed, causing this disruption in redox equilibrium (ROS). The control of cellular differentiation, communication, and their existence, as well as tissue homeostasis, depend greatly on ROS. Furthermore, ROS controls the homeostasis of cells and plays a crucial role in the development of disease by regulating the mechanisms by which cells malfunction. Abnormally high levels of ROS promote the formation and spread of cancer, as well as other unfavorable processes (Figure 8.1). Because ROS has both pro- and anti-tumorigenic actions, it plays both a negative and a positive role in the biology of cancer. Increased ROS and RNS levels, which are commonly associated with persistent inflammation, cause a range of epigenetic changes, DNA mutations, and genomic instability. All these changes support the genesis, growth, progression, metastatic spread, and treatment resistance of tumors.

It has long been recognized that inflammation and the emergence of cancer are related [36]. The body's defenses against germs are coordinated by the inflammatory response, which also regulates tissue regeneration and repair that can occur after either infectious or non-infectious tissue injury. According to epidemiological data, chronic inflammation causes dysplasia, which in turn increases the risk that cancer may spread [37].

A small tumor can collect adequate oxygen and nutrients from its environment when it first develops from a few stray cells. Yet, as it expands,

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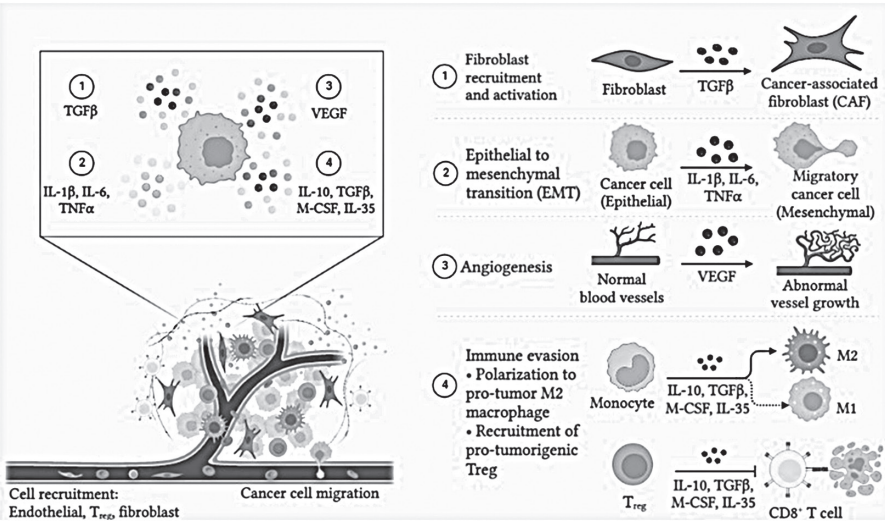

FIGURE 8.1 Overview of cancer associated changes.

supply begins to fall short of demand, leading to an abnormal situation. The cancer cells generate chemical signals that encourage immune cells such as macrophages and granulocytes to colonize the tumor as they struggle to survive and as they acquire more and more genetic flaws [38]. When these cells reach the tumor's interior, they release substances known as cytokines, which trigger the angiogenesis process, resulting in the inflow of vital nutrients and oxygen. Other cytokines promote the formation of the stroma, which acts as a cellular "cushion" for the tumor. As a result of chemicals (free radicals) released by other inflammatory cells, the tumor's DNA is further damaged. With the release of molecules that aid tumor cells in separating from their environment, inflammation may also serve as the catalyst for metastasis. Combined, these results show how cancer development is enhanced by inflammation that is being controlled by growing tumors.

Table 8.3 summarizes the role of ROS and inflammation in cancer.

8.5 ROLE OF PROBIOTICS IN OXIDATIVE STRESS AND INFLAMMATION

The body's reactive oxygen species are intimately related to biological aging. It is possible for free radicals to damage DNA, proteins, lipids, and other molecules of cells, causing gradual physiological decline and diseases

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TABLE 8.3 Role of ROS and Inflammation in Cancer

Effect	Mechanism	References
Inflammation and Tumor	Myeloid cell infiltration may enhance the mutational load of existing neoplasms because ROS have been demonstrated to cause DNA damage in epithelial cells *in vitro*.	[39]
	The higher cancer risk in those with conditions like Crohn's and inflammatory bowel disease may be explained by the possibility that myeloid cell-derived ROS cause driver mutations.	[40]
	Tumor growth is enhanced in wounded limbs by the induction of paracrine factors such as TGF-β and bFGF in wound fluid.	[41]
	Administration of the phorbol ester TPA and the mutagen DMBA causes skin tumors.	[42]
	Hepatocellular carcinoma caused by a mutagen after diethyl nitrosamine (DEN) administration.	[43]
	Chronic inflammatory circumstances can cause myeloid cells to create ROS, which can promote the development of cancer.	[44]

such as cancer and cardiovascular disease [45]. A rise in oxidative stress is widely believed to be associated with cancer, diabetes, Parkinson's disease, Alzheimer's disease, cardiovascular disease, neurological disorders, and psychiatric disorders. Oxidative stress occurs due to an imbalance in the body's prooxidant/antioxidant status, which is normally regulated by the liver. The past few years have seen a rise in interest in probiotics due to their potential to treat diseases caused by inflammation. Probiotics may successfully lower both peripheral and central inflammation through a variety of routes, according to several studies. The root cause is connected to gut flora restoration, increased gut permeability, immune system regulation, and reduced pro-inflammatory cytokine production [46]. Additionally, probiotics have beneficial effects on a number of diseases, including inflammatory bowel disease, obesity, and neurodegenerative conditions. They can control the maturation and activity of microglia and possibly stop neuroinflammatory processes. In addition, it has been found that probiotics and/or bacterial metabolites can influence the amount of endogenous and exogenous ROS produced by the host, leading to an improvement in oxidative status. In the gastrointestinal tract, there are ten times as many bacteria as human cells, and their genomic content exceeds 3 million, compared to 23,000 genes in the human genome [47]. Research over time has shown that probiotic *Bifidobacteria* and *Lactobacilli* strains have antioxidant capabilities.

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8.5.1 PROBIOTICS AND OXIDATIVE STRESS

The current study looked at a number of publications from clinical trials that examined how probiotics affected oxidative stress and redox potential in studies involving humans. According to studies, probiotics strengthen the body's antioxidant function and promote oxidative stability. In clinical studies, malondialdehyde (MDA), 7,8-dihydroxy-8-oxoguanosine (8-OXO-G), glutathione (GSH), superoxide dismutase (SOD), nitric oxide (NO), catalase (CAT), and glutathione peroxidase (GPx) were primarily evaluated [48]. Probiotic supplementation's impact on TAC was examined in randomized studies. According to the preliminary and main meta-analysis findings, probiotic medicines significantly raised TAC levels in blood by 52.46 mmol/L [49]. The quantity of TAC in the body is influenced by a variety of enzymatic and non-enzymatic variables. These elements can make up the body's antioxidant structure by fending off oxidizing agents. The presence of vitamin E, SOD, and glutathione are the major components of the TAC structure [50]. It has been demonstrated that different probiotic species can control inflammatory and immunological responses in the host by changing the makeup of the gut microflora [51]. Probiotics work to increase TAC by boosting GSH levels, scavenging superoxide and hydroxyl radicals, and decreasing inflammatory IL-6 expression [52]. Considering the findings of this research, patients with diabetes or gestational diabetes who supplement with probiotics or synbiotics experience a reduction in blood sugar or insulin levels, as well as improvements in insulin resistance and HbA1c. Research on TAC has shown the benefits of probiotic supplementation on blood glucose in these individuals [53]. As high levels of insulin and insulin resistance are associated with elevated levels of oxidative and inflammatory factors, probiotic supplementation appears to reduce the level of insulin resistance by lowering blood glucose, insulin, and oxidants in the body, as well as increasing TAC.

8.5.2 PROBIOTICS AND INFLAMMATION

It has been demonstrated that different probiotic strains have a variety of impacts on the human body and its defenses. In numerous *in vitro* and *ex vivo* models, as well as in mouse models, their crucial function in the control of inflammation has been thoroughly described. These models demonstrate the catastrophe of the immune regulatory networks in blood circulation, which sets off a chain of actions that result in an inflammatory reaction. Certain types of bacteria can influence the intestinal mucosal barrier, the

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gastrointestinal luminal environment, and the mucosal immune system. Probiotics may have an impact on a variety of innate and acquired immune system cells, including monocytes, killer cells, macrophages, lymphocytes, and epithelial cells (Figure 8.2). The pattern recognition receptors (PRRs) expressed on immune cells and non-immune cells, like M cells in Peyer's patches and intestinal epithelial cells, may be specifically activated by them. TLRs, which may trigger signaling cascades that result in cell proliferation and the release of cytokines to control the immune system, are the PRRs that have been the subject of the most research.

Additionally, some particular strains secrete substances that could cause the immune system to become activated. M cells specifically phagocytose

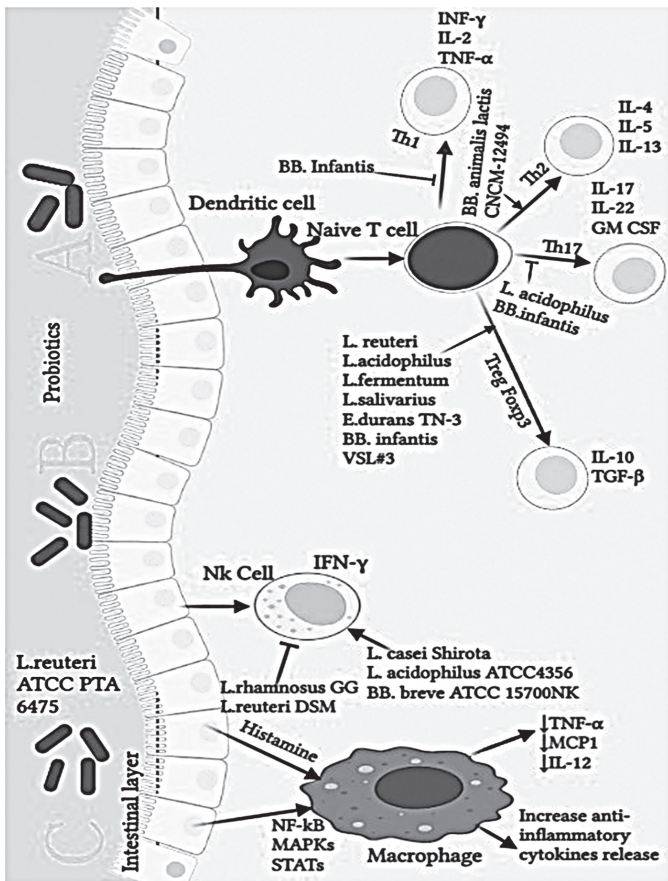

FIGURE 8.2 Representation of GI-based probiotic immune-modulating pathways A. Naïve T- Cells, B. NK cells C. Immune cells like MAP kinase cascade, STATs and NF-kB.

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or internalize the probiotic and the antigenic components derived from its metabolites to generate endosomes. Certain probiotic strains can cause dendritic cells to become activated, which then transport antigens to nearby lymph nodes and release IL-10 and IL-12. Here, dendritic cells use their arsenal of cytokines to encourage naïve T and B cells to differentiate into their respective subpopulations. In more detail, naïve Th cells can develop into Treg, Th1, and Th2 immune cells, while B cells can change into plasma cells that are actively involved in humoral responses or regulatory B (Breg) cells that produce IL-10 or TGF. In addition, by producing cytokines like IL-12 and IL-15, dendritic cells could promote the activation of NK cells. Many lactic acid bacteria, in particular, encourage the IFN-γ synthesis by NK cells through dendritic cells in the presence of other probiotic microorganisms.

TABLE 8.4 Probiotics in Control of Inflammation

Probiotic Strain	Model Used for the Study	Cytokines and Inflammatory Mediators Involved	Reference
L. acidophilus	DSS-induced colitis in mice	IL-17, IL-23, TGF-β1, TNF-α	[54]
L. reuteri ATCC PTA6495	TNBS-induced colitis in mice	IL-1β, IL-6	[55]
E. durans TN-3	DSS-induced colitis in mice	Treg, IL-10, IL-1β, IL-6, IL-17A, IFN-γ	[56]
L. rhamnosus RC007	TNBS-induced colitis in mice	IL-10/TNF-α ratio	[57]
L. casei Lbs2	TNBS-colitis-induced in mice	Treg	[58]
L. fermentum CECT5716, *L. salivarius* CECT5713	DSS-induced colitis in mice	IL-1β, IL-12, TGF-β, NOS	[59]
BB. infantis	Colorectal cancer induced by dimethyl-hydrazine in mice	IL-2, IL-12, IFN-γ	[60]
B. breve DM8310, *L. acidophilus* DM8302, *L. casei* DM8121, *S. thermophilus* DM8309	5-FU-induced mucositis in mice	IL-6, TNF-α	[61]
L. acidophilus	DSS-induced colitis in mice	Treg, IL-10, IL-17	[62]

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TABLE 8.4 *(Continued)*

Probiotic Strain	Model Used for the Study	Cytokines and Inflammatory Mediators Involved	Reference
L. fermentum CQPC04	DSS-induced colitis in mice	IL-10, TNF-α, IFN-γ, IL-1β, IL-6, IL-12, NF-κBp65, COX-2	[63]
L. plantarum CAU1055	DSS-induced colitis in mice	TNF-α, IL-6, NOS, COX-2	[64]
L. plantarum C88	Aflatoxin B1-induced liver injury in mice	IL-1β, IL-6, IL-8, TNF-α, IFN-γ, NF-κB	[65]
L. lactis ML2018	DSS-induced colitis in mice	NF-κB, MAPK	[66]
L. reuteri LMG P-2748	*C. difficile*-induced colitis in mice	IL-10	[67]

According to studies, the immunological modulation brought on by probiotic bacteria may be caused by the anti-inflammatory cytokines secreted in the stomach. However, the precise molecular interactions between the host and the probiotics are not well understood. The three genera *Bifidobacterium* (*BB*), *Bacillus* (*B.*), and *Lactobacillus* (*L.*) are the most often utilized probiotics in humans, but the genus *Saccharomyces* (*S.*) is also frequently employed in commercial goods [68]. *Bifidobacterium* causes the acquisition of tolerance, whereas some strains of *Lactobacillus* might modify the cytokine generation by immune cells.

Each probiotic strain exhibits such distinctive regulatory behaviors, which are related to their structure, the range of mediators they release, and the numerous pathways they concurrently activate [69]. Probiotics' ability to reduce inflammation has been examined *in vitro*, *ex vivo*, and in animal studies to assess cytokine generation and immune cell propagation. We discuss current research topics that show certain probiotic strains have an anti-inflammatory impact in the sections that follow (Table 8.4).

8.6 PROBIOTICS IN THE PREVENTION OF CARCINOGENESIS

The World Health Organization and the Food and Agriculture Organization of the United Nations define probiotics as live bacteria that, when supplied to a host in a suitable proportion, confer an advantage for health [70]. Figure 8.3 illustrates the mechanism of action of probiotics.

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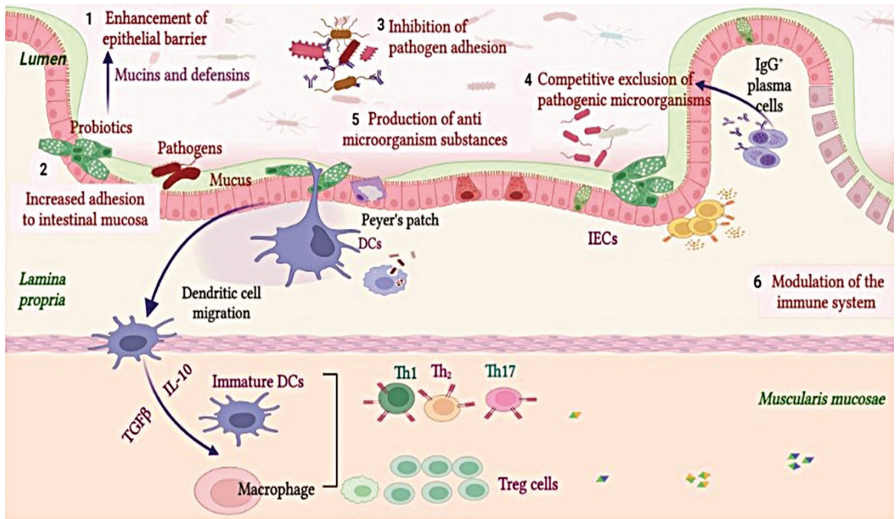

FIGURE 8.3 Mechanism of action of probiotics.

For the body to remain in a state of equilibrium, the gut microbiota can be crucial. Interruption of disease processes, such as cancer, and pro-inflammatory immune reactions might result from an imbalance in the gut microbiota. The probiotic's efficiency in preventing, treating, and supporting cancer is examined using the most recent findings in scientific research [71]. One of the first to point out a link between a diet rich in *Lactobacillus* and a 37% reduction in the risk of colorectal cancer compared to controls was Goldin and Gorbach [72]. Probiotics may benefit cancer cells by controlling their development and mortality, according to the results of numerous *in vitro* investigations on myeloid leukemia, gastric, colon, and other cancer cells. The majority of *in vitro* studies using human colon cancer cells were performed. One of the key mechanisms underlying the antagonistic effects of probiotics on various microorganisms is the modification of the gut microbiota. Other significant mechanisms include competitive adhesion to the mucosa and epithelium, strengthening of the gut epithelial barrier, and immune system modulation to the host's advantage [73].

8.6.1 POTENTIAL MECHANISMS BY WHICH PROBIOTICS PREVENT CARCINOGENESIS (FIGURE 8.4)

1. **Modification of the Composition of the Gut Microbiota:** To maintain eubiosis, the gut microbiota needs to be appropriately

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diverse and balanced. An imbalance among harmful and beneficial microbes in the intestinal microbiota is known as dysbiosis. The risk of developing colorectal cancer is further increased by dysbiosis, resulting in chronic inflammation and increased synthesis of carcinogenic substances [74]. Probiotics are advantageous for the host by increasing intestinal barrier integrity, lowering pathogen development, and slowing the metabolism of chemicals that promote cancer.

2. **Intestinal Microbiota Metabolic Activity:** Numerous bacteria found in the human gut are capable of producing endogenous bile salts as well as tumor-causing compounds from dietary sources. These substances can have genotoxic and cytotoxic effects, leading to unusual colonocyte growth and the stimulation of anti-apoptotic pathways, which aid in the progression of colon cancer. By modulating the functioning of such digestive enzymes, probiotics can change bacterial metabolism and reduce the risk of colon cancer. Probiotics can cause cell lysis, interfere with or inhibit the synthesis of DNA, proteins, and RNA, and cause the transmembrane potential to dissipate as well as the leakage of K^+ ions, ATP, and amino acids from the cytoplasm of the attacked cells in sensitive microorganisms. Bacteriocins produced by probiotics can be lethal or bacteriostatic and impact bacterial cell membranes with receptors that may adhere to them, causing cell death [75].

3. **The Generation of Substances Having Anticarcinogenic Properties, Including CLAs and SCFAs:** Although short-chain fatty acids (SCFAs) have immunomodulatory properties that influence inflammation, conjugated linoleic acids (CLAs) regulate the proliferation of genes that control apoptosis (Bcl-2, caspase 3 and 9) and the response of cells to proliferation factors. Additionally, colonocytes' ability to produce eicosanoids can be suppressed by CLAs [76].

4. **Suppression of Cancer Cell Growth and Induction of Apoptosis:** The rate at which cancer develops is influenced by the apoptosis and proliferation of cancer cells. Cancer cells experience greater proliferation than apoptosis as the malignancy develops. Since apoptosis doesn't affect nearby cells or result in inflammation, cancer cells can be eliminated less violently. Bcl-2 and Bcl-xl, two NF-κB-dependent genes that regulate cell viability and proliferation, may be inhibited by probiotic bacteria such as lactic acid bacteria (LAB), working to prevent cancer [77].

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5. **Impact on Additional Mutagenic and Carcinogenic Factors:** Free radicals and cancer-causing substances are less active when probiotics are present because they can change the functioning of many enzymes involved in the detoxification process. Probiotics can impact other mutagenic and carcinogenic factors, helping prevent cancer and contributing to overall health. Probiotics modify microbial enzyme activity in the intestines through various mechanisms, including their capacity to create acids that might decrease the pH of the colon, synthesize antibiotic substances that hinder the spread of other microbes, and exclude infectious microbiota [78].
6. **Degradation and Binding of Cancer-Causing Substances in the Gut Lumen:** Carcinogenic compounds may adhere to the cell walls of some probiotic bacteria. A cationic exchange between the cancer-causing agents and the peptidoglycan molecules found within their cell walls might take place. Through the feces, microorganisms and potentially cancer-causing chemicals would be eliminated similarly [79].
7. **Immunomodulation:** For the lymphoid tissues of the body's immune response to develop, the body's immune response must be activated by the microbes in the gut microbiota. These microbes induce and maintain immune responses against bacterial and viral infections, environmental antigens (food and inhalation), and prevent autoimmune and allergic reactions. The intestinal microbiota, which contains probiotic bacteria, has immunomodulatory action through these three seemingly incompatible processes [80].
8. **Strengthening the Intestinal Barrier:** The intestinal barrier and permeation can be altered by the microbes in the gut microbiota. Probiotics can decrease intestinal permeability due to their potential to alter the intestinal barrier's constituents, including intracolonic pH, mucin formation, and cellular junction proteins. A more acidic (lower intracolonic pH) environment prevents the growth of putrefactive and pathogenic microbes along with microbial enzymes that produce cancer-causing substances. When the incubation medium's pH was acidic, inhibition occurred, but there was no growth inhibition when it was neutral.

Figure 8.4 depicts the mechanisms of probiotics in prevention of carcinogenesis.

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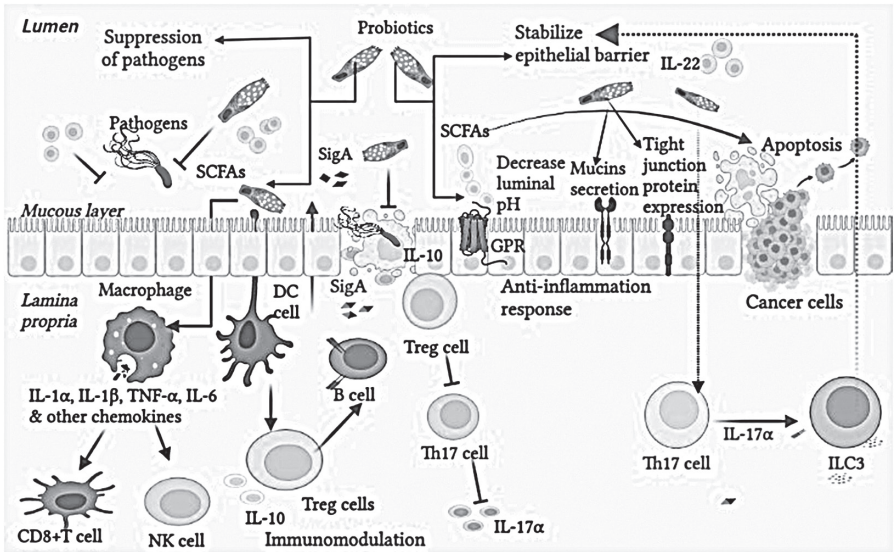

FIGURE 8.4 Potential mechanisms of probiotics in prevention of carcinogenesis.

8.7 CLINICAL TRIALS IN PROBIOTICS FOR DECREASING ROS

When reactive oxygen species (ROS) are formed in surplus or are not cleaved enough, it results in oxidative damage, which can lead to DNA damage, lipid peroxidation, enzyme inactivation, cell necrosis, and apoptosis [81]. Interventional research [82-85] has looked at how probiotic supplementation affects oxidative stress reduction and antioxidant biomarker improvement. The effects of probiotic and synbiotic supplementation on oxidative stress indices in healthy participants were also studied in a meta-analysis, and the scientists concluded that these products enhance antioxidant resistance and boost the body's supply of antioxidant enzymes [86]. One more meta-analysis of individuals with Chronic Kidney Disease (CKD) revealed that bacteriological therapies significantly decreased blood levels of C-Reactive Protein (CRP), Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), and Total Glutathione (GSH) [87]. A recent comprehensive analysis found that probiotic administration may reduce oxidative stress and systemic inflammation in people with diabetic nephropathy (DN) without having any appreciable negative effects [88].

8.7.1 CLINICAL STUDY

In one investigation, the impact of several *Lactobacillus* strains on athletes' oxidative stress was assessed [89]. In this study, one group drank

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Lacticaseibacillus paracasei IMC 502 and *Lacticaseibacillus rhamnosus* IMC 501 daily over the course of four weeks. Both bacterial strains were tested at the beginning of the study using the thiobarbituric acid (TBA) technique to measure oxidative stress resistance and identify *in vitro* antioxidative activity. Thus, the antioxidative impact of both *Lactobacillus* strains, which mostly manifests in intracellular extracts, was proven by the same linoleic acid peroxidation suppression in comprehensive cells. Furthermore, both strains have adequate tolerance to oxidative stress. The biological antioxidant capacity of plasma, as well as the quantity of blood reactive oxygen metabolic compounds, was next assessed in the probiotic and control groups. Members were asked to engage in vigorous physical exercise, which increases oxidative stress and ROS generation.

It was observed that the two strains under investigation have significant antioxidant potential. Probiotic supplementation helps raise plasma antioxidant levels, which neutralize ROS and present a fantastic potential for probiotic application on a larger scale. Analysis of the feces following probiotic treatment further indicated that these bacteria's capacity for colonization is probably host-specific. Other studies' findings support the positive effects of probiotics [90]. In this intricate and thorough investigation, healthy volunteers' responses to probiotic pills and fermented goat milk comprising *Lactobacillus fermentum* ME-3 were evaluated for their antioxidant potency. Total antioxidative status (TAS), glutathione redox fraction, and total antioxidative activity (TAA) of participants' blood serum were examined to assess the oxidative status of the human body. Probiotic pills and fermented goat milk both showed improvements in oxidative stress indicators.

However, the TAA and TAS indicators were found in considerably greater concentrations in the *Lactobacillus fermentum* ME-3 fermented goat milk cluster compared to the capsule group. Moreover, a decline in the glutathione redox fraction was seen, nonetheless only in those who had fermented goat milk. The present suggests that there may be a connection between the formulation type and the effects of probiotic antioxidants within the host. Further research, however, does not support probiotics' beneficial effects on oxidative stress. The fast production of physiological amounts of ROS against an unidentified source by some classes of commensal gut bacteria in human epithelial cells has regulatory consequences [91-94]. NADPH oxidases' catalytic activity is frequently used to create cellular ROS. Furthermore, it was shown that lactobacilli are particularly strong inducers of ROS formation both *in vivo* and in cultured cells. This impact was established, in accordance with Neish [95], by an upsurge in the oxidoreductase response of transcription

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factor stimulations (NF-κB), Nrf2, and the antioxidant response element, demonstrating a controlled cell response to enhanced ROS generation.

The third trimester of pregnancy was the subject of another investigation. Contrary to normal yogurt, probiotic yogurt enhanced through *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12 had not substantially altered serum 8-oxo-G levels, erythrocyte GPx, plasma GSH, or TAC levels after nine weeks of consumption [96]. Only the level of erythrocyte glutathione reductase (GR) increased considerably from the control group.

In accordance with probiotic supplementation, Chamari et al., [97] evaluated the amount of CAT in the plasma of healthy women. In comparison to the untreated or control groups, the probiotic clusters exhibited a statistically significant rise in catalase levels. In contrast to placebo, *Lactobacillus casei* 01 supplements had not significantly enhanced oxidative status in rheumatoid arthritis patients [98]. Finally, a sample of smokers was studied to see if probiotics had any positive benefits. Plasma F2-isoprostane concentrations were significantly lower (31%) after *Lactobacillus plantarum* supplementation compared to the control group. These biochemical indicators can accurately and efficiently detect oxidative stress and lipid peroxidation [99] (Table 8.5).

TABLE 8.5 Clinical Studies

Strains	Study Groups	Main Conclusion	References
Lactobacillus paracasei IMC 502 and *L. rhamnosus* IMC 501	Athletes	Exert strong antioxidant activity	[89]
Lactobacillus fermentum ME-3	Healthy volunteer	Increases counts of intestinal lactobacilli and reduces oxidative stress	[90]
Lactobacillus acidophilus LA5 and *Bifidobacterium lactis* BB12	Pregnant women	Do not affect oxidative stress markers, only significantly increase erythrocyte GR level	[96]
Lactobacillus acidophilus LA5 and *Bifidobacterium lactis* BB12	Healthy women	Consumption of selected probiotic strain increases antioxidant enzyme levels and decreases oxidative stress	[97]
Lactobacillus casei 01	Rheumatoid arthritis patients	No significant improvement of oxidative status	[98]
Lactobacillus plantarum 299v	Healthy smokers	Reduction of plasma F2-isoprostane concentrations	[99]

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Forty patients with a brucellosis diagnosis, between the ages of 8 and 15, were registered in a randomized, double-blind, and placebo-controlled experiment. Probiotic supplements or placebos were given to study participants in one of two groups (n = 20 per group) over an eight-week period. To measure biochemical markers, plasma specimens were taken beforehand and subsequently after the 8-week intervention. A pediatric infectious disease expert assessed the clinical state. Probiotic supplementation after the 8-week intervention markedly increased malondialdehyde ($P < 0.001$) and overall antioxidant capacity ($P < 0.001$). Although probiotic intake had no statistically significant impacts on highly sensitive CRP, total glutathione, and other experimental conclusions related to placebo, there was a variance between the probiotic group and the placebo group for the duration of fever ($P < 0.02$) and musculoskeletal pain ($P < 0.001$), respectively. Overall, probiotic supplementation had a positive effect on clinical status and the body's natural antioxidant defenses in pediatric brucellosis patients [98].

Another double-blind, randomized controlled study with forty critical care unit admissions was conducted. For seven days, they were arbitrarily allocated to either a probiotic or a placebo. Acute Physiology & Chronic Health Evaluation records, malondialdehyde (MDA), total antioxidant capacity, and CRP levels in serum were assessed prior to the study's start and on day seven. By the conclusion of the trials, a notable disparity existed ($P = 0.003$ and 0.001, respectively) between the two groups' CRP levels and APACHE II scores. TAC and MDA levels had not varied significantly between the two groups. Probiotics were given to very unwell individuals, which decreased inflammation and improved clinical outcomes. The indicators of oxidative stress did not, however, vary significantly [99].

8.8 FUTURE ASPECTS AND CONCLUSION

In addition to being naturally occurring byproducts of distinct cellular compartments' metabolic processes, ROS also operate as signaling molecules that control particular biological processes essential to healthy cell function and survival. The pathogenesis of a disease can, however, be affected by deregulation of ROS signaling or excessive generic ROS generation. The importance of ROS in cell metabolism and inflammatory signaling has been underlined in this study. Therefore, it is not unexpected that disorders connected to metabolic dysregulation and inflammation also involve ROS significantly.

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There are several areas that need more research. It's significant that whereas cytoROS and mitoROS signaling have received a lot of attention, less is known about the role of ROS produced by peroxisomes and the endoplasmic reticulum in maintaining cellular homeostasis. To better understand the role of organelle/compartment-specific ROS and its impact on important cell processes like fatty acid biosynthesis, protein translation systems, and post-translational modifications, novel organelle-targeted probes and antioxidant substances will be used. Due to the connection between inflammatory and metabolic signaling, such techniques will correspondingly shed light on how reactive oxygen species involved in inflammatory signaling might influence and be influenced through this pathway. Additionally, investigation must continue to define the tissue-specific function of ROS signaling in metabolism and cardiac illnesses in light of the emergence of tissue-specific and inducible transgenic mouse models and Cre-lox technologies. Understanding tissue-specific redox signaling would be vital in our endeavor to discover novel and innovative medicines to treat disease. The etiology of cardiovascular and metabolic diseases is complicated. Understanding the role and impact of ROS on metabolism is an intriguing topic for scientific investigation because metabolic dysregulation is a major contributor to cellular dysfunction and the development of disease [100].

Within biological systems, ROS and free radical behavior have become more complicated. Free radicals and ROS were formerly thought to be harmful; however, modern mechanisms describe both beneficial and harmful effects. With the onset of reperfusion and in relation to damage, a burst of ROS has been well documented. Yet, ROS could also act as a signaling preconditioning defense and trigger stress reactions that aid in survival. It is known that ROS synthesis occurs through ischemia, even with the short oxygen tension from a source that is most likely the mitochondria, and reactive oxygen species-induced ROS release might intensify its signal. Unidentified cellular sources may be responsible for the burst of ROS observed after reperfusion, which differs from the source detected during ischemia.

Energy metabolic processes, survival/stress responses, apoptosis, inflammatory responses, oxygen sensing, and many other important processes are all controlled by ROS and cellular redox conditions. Even though cellular systems may exhibit reperfusion damage, whole organ and animal models continue to show conflicting findings on reperfusion injury and the therapeutic value of antioxidants. Together, these findings may shed light on why therapeutic trials of antioxidants have shown such inconsistent and generally unfavorable outcomes. Imminent antioxidant therapies are likely to be successful; however,

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they should: be more specific for the site of action; not have negative effects on other signaling pathways; be targeted to a specific ROS or cellular compartment; and be "time-sensitive" so they provide the right treatment at exactly the right moment in ischemia and other conditions [101].

The efficacy of probiotics' antioxidative intrusion for a certain clinical state depends on careful assessment of the most suitable species and strains. Probiotics can be "potentially" useful in a number of conditions, yet the European Food Safety Authority hasn't approved any health claims on them [102]. By lowering lipid peroxidation and ROS production while enhancing SOD activity, probiotics may be able to treat ischemia-reperfusion damage. Irritable bowel syndrome may be another condition that probiotics might help. The most popular strains are Lactobacilli and Bifidobacteria, which are said to release SOD enzymes as well as metal-complexing and antioxidant compounds. These strains may also shield the bowel from IBD and even colorectal carcinoma. Probiotic bacteria with the ability to provide SOD locally may offer a novel treatment choice for bowel illness with more ROS formation. The antioxidant properties of probiotics can also help individuals with liver illness that is marked by severe oxidative stress. The hunt for particular probiotic species that provide the best anticipation and justification of oxidative stress must go on if new probiotic products are to be created with the capacity to prevent it. To fully understand the probiotics' antioxidative potential, further research is also required.

KEYWORDS

- **Probiotics**
- **Reactive Oxygen Species (ROS)**
- **Inflammation**
- **Polymorphonuclear neutrophils (PMNs)**
- **Gut dysbiosis**

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