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Optimum health and inhibition of cancer progression by microbiome and resveratrol

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1. ABSTRACT

Resveratrol (RES) is a naturally occurring polyphenol found in fruits, green leafy vegetables, and peanuts. This versatile compound, which has potent regenerative, anti-oxidative, and cancer-fighting properties, is produced in plants, particularly in response to stress stimuli. By various mechanisms, including regulation of genes and proteins, RES inhibits the growth of pathogenic bacteria and the development of cancers. The gut has a prominent role in nutrient assimilation, metabolism, immunity, and cancer regression, and the endogenous microbiome protects the host from invasive bacteria that facilitate the progression of various diseases. Short-chain fatty acids (SFCAs) are the byproducts of microbial fermentation in the gastrointestinal tract. Native microflora regulates internal homeostasis, influence the activity of host immune cells, and regress some cancers via the

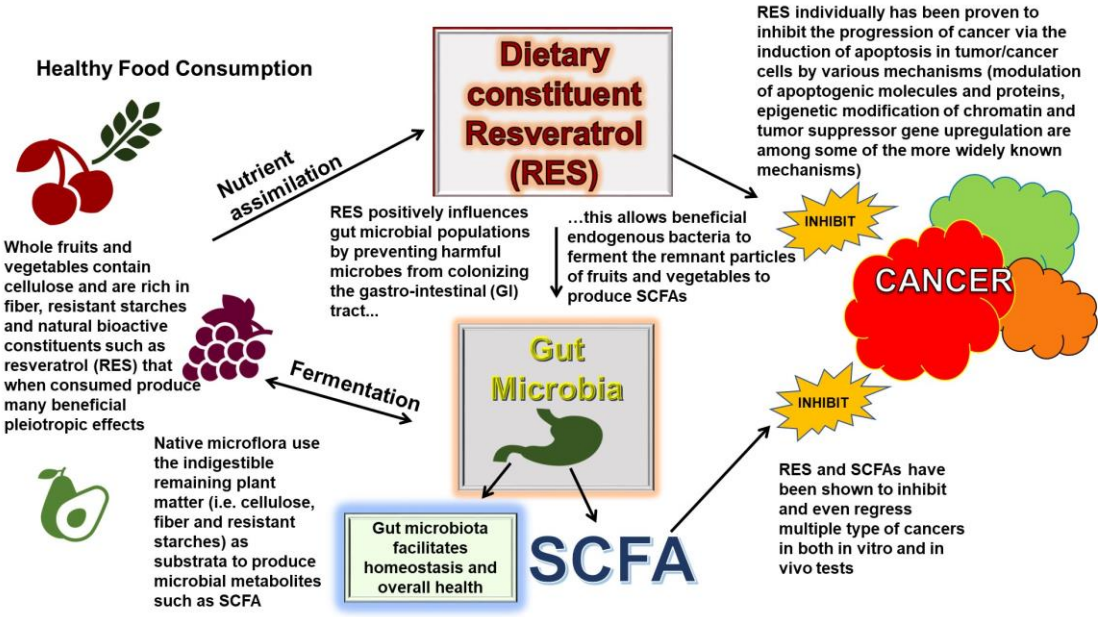

Figure 1. The figure is a schematic flow chart that illustrates how RES, a dietary constituent of red fruits such as red grapes and a select group of vegetables influence or modulate the activity of native microflora to produce beneficial metabolic byproducts such as SCFAs.

action of SCFAs produced from a plant-based diet. This review shows the relevance of dietary constituents and gut microbial activity in ensuring optimal health of the host.

2. INTRODUCTION

Cancer, a public health problem affecting the populations of many industrialized nations, is the second leading cause of death in the United States. According to data compiled by the National Center for Health Statistics (NCHS), the National Cancer Institute (NCI), and the Centers for Disease Control and Prevention (CDC), there will be, in 2019, an estimated 870,970 new cases of cancer (at all sites of the human body) for men and 891,480 new cases of cancer for women. Sadly, the same agencies predict that, in this year, there will be approximately 321,670 and 285,210 deaths for men and women, respectively (1). Some of the most common forms of cancer expected to be diagnosed among men and women are those of the prostate, lung, breast, and colon. Prostate cancer accounts for nearly 1 in 5 new diagnoses for men, and breast cancer is responsible for a third of the new diagnoses for women. Traditional treatment methods (i.e., chemotherapy and/or surgery) are only moderately effective, have undesirable side effects, and can even accelerate the progression of the cancers (1).

Less invasive and more natural alternatives for cancer treatment are needed. Two promising alternatives are RES, a polyphenolic compound found in plants, and short-chain fatty acids (SCFAs), the metabolic byproducts of intestinal microbes. These compounds curtail the growth of various malignant tumors (2, 3). RES is found in some wild plants and in various foods, including red grapes (a major constituent of red wine), berries, vegetables, and peanuts. This bioactive compound has powerful anti-oxidative, anti-inflammatory, anti-aging, and cancer-fighting properties (4-9). It protects the plants that produce it from invasive pathogenic organisms. Endogenous microbes often utilize indigestible starches, cellulose, and fiber from plant-based foods to produce SCFAs. The three most prominent SCFAs found in the intestinal lumen are acetic, butyric, and propionic acids. These microbial metabolites modulate various mammalian biochemical/biological processes, including nutrient assimilation, metabolism, immune system regulation, and cancer inhibition and regression. The gut is a mediary of health and homeostasis (the Figure 1 below provides an overview of how the bioactive dietary

compound RES both mediates and works in tandem with the host's native microflora to facilitate this process and produce important metabolic byproducts such as SCFAs); disturbances in the composition of the native microflora can facilitate infections and colonization by pathogenic organisms and lead to diseased states. RES and SCFAs, among their other beneficial properties, help to maintain a homeostatic internal environment by inhibiting the virulence and pathogenicity of exogenous microorganisms This review of RES and SCFAs examines their disease-fighting properties and explores the causal relationship that diet and native microbial activity have on cancer risk and overall health.

3. THE INTESTINAL MICROBIOTA

Research has begun to focus on the role of commensally endogenous bacteria in mediating human metabolism and immunity. The human body operates in tandem with an array of microbes that form a complex community mirroring highly dense and biodiverse ecological systems. These ecosystems are composed of bacteria that surpass, in number, the total of human cells (10-12). Microbes are acquired early in the human developmental cycle, but it is debatable as to when this process begins. Nevertheless, when they are acquired and established on and within the human body, they begin to facilitate a variety of host physiological functions, including nutrient assimilation and defense. Perhaps the most studied microbe-human host interaction occurs within the gastrointestinal (GI) tract. Located along the intestinal epithelia and on the membranes of host immune cells, such as macrophages and neutrophils, are proteinaceous structures known as pattern recognition receptors. These specialized sensory structures recognize evolutionarily conserved microbial metabolites such as lipopolysaccharides, peptidoglycans, and microbial nucleic acids, and subsequently recruit host immune cells to the areas of infection and inflammation (13-16). The gut microbiota are involved in maintaining the health and viability of the host. The metabolic activity of the microbiome, specifically within the gut, regulates host gene expression downstream of the recognition site. Changes in the microbial composition and its related activity can lead to conditions such as colitis and colon cancer. For instance, mice deficient in the *NLRP6* gene, which expresses the corresponding inflammasome (a protein complex that detects infection and cellular injury), have an altered gut microbiota characterized by an overabundance of Prevotelleceae bacteria. As a result, this increases colitis severity, which can ultimately lead to the onset of colon cancer (17-22). Other research highlights a factor that contributes to the development of Crohn's disease. *Nod2* knockout mice are more vulnerable to colonization by intestinal pathogens due to a dysbiosis of host-microbe interactions. Mice with normal *Nod2* expression are characterized by normal host-microbe interactions; the colonization of such pathogens is not evident. Thus, certain microbial populations must be present in the intestine for the *Nod2* gene to be properly expressed (10-14, 21). Such interactions are typical for a healthy host organism. Current research confirms the importance of the microbiome in the life of the host. There is now a link between what one consumes and the manifestation of chronic conditions such as heart disease, diabetes, and cancer. In industrialized societies, these endemic health problems are prominent because of a low-nutrition diet containing primarily processed food.

The wave of health consciousness that has gripped a growing segment of society has spurred researchers to rethink old paradigms concerning health and medicine. Two growing areas of research have begun to shed light on possible treatment alternatives, which involve the effect of endogenous gut microbial metabolites (microbe-associated molecular patterns, MAMPs) on host immunity and the utilization of naturally occurring compounds, particularly RES, which inhibits and reverses the progression of various cancers. RES, a polyphenolic compound found in the skins of select fruits and vegetables, protects plants from invasive pathogenic organisms. Clinical data demonstrate that RES prevents the progression of various cancers. The gut is a large interface between a host organism and its external environment. Microbes that reside within the human GI tract produce metabolites from the catabolic breakdown (i.e., fermentation) of substrates such as starches and dietary fibers from consumed meals; these metabolites are commonly referred to as MAMPs. A group of MAMPs of particular relevance are microbial metabolites, short-chain fatty

acids (SCFAs). These provide pleiotropic physiological benefits, including the regulation of colonic epithelial cell metabolism/homeostasis, efficient nutrient assimilation, reversal of inflammation (via immune cell activity), and the inhibition of some cancers.

4. MICROBES AND THEIR METABOLIC BYPRODUCTS, SCFAS, AFFECT HOST HEALTH, BIOLOGICAL FUNCTIONALITY, AND IMMUNITY

The benefits that commensal microbes have on metabolism are well-documented. The GI tract is home to a complex and intricate ecosystem. The many folds and oscillations of the GI tract make it a large interface between an organism and its outside environment. An adult GI tract is estimated to have an area of 150-200 m^2. Approximately 233 human proteins are homologous with those in bacteria, suggesting that we have acquired these genes from the resident microflora. Microbial activity can directly or indirectly impact human health and internal balance, and dysbiosis amongst endogenous microbial populations can facilitate the colonization of pathogenic microorganisms. The byproducts of microbial activity in the GI tract can affect internal balance and immunological responses of the host. Microbial byproducts, namely SCFAs, act as ligands for activated/target cellular receptors expressed on the membranes of specific host tissues and immune cells to initiate a variety of immune responses, including the prevention and/or reversal of multiple types of cancers (11, 12, 16, 17).

Investigations concerning SCFAs and their potential effects on the overall health and nutrient metabolism of the host are focused on creation of a profile highlighting the microorganisms responsible for producing the byproducts/activity responsible for such beneficial effects. Researchers have examined the microbiota within the GI tracts of obese and lean mice to assess the similarities and differences between their native microbial populations. The rationale behind such research is that, if there are consistent differences among the bacterial populations between the two test groups, researchers can conclude that the health effects are due, at least in part, to the presence or absence of the selected bacterial species, which have been affected by the diet of the test groups. Obese specimens exhibited a 50% reduction in the population abundance of Bacteroidetes, microbes that are primarily responsible for producing acetic and propionic acids. Conversely, Firmicutes were present in higher numbers in obese mice compared to the lean specimens. Obese mice also had higher concentrations of SCFAs within their GI tracts. This led researchers to conclude that these differences could affect energy harvesting and metabolism in animals. To confirm this hypothesis, researchers set up an experiment in which they fed wild-type obese mice either a high-fat or low-fat diet and analyzed the cecal SCFA concentrations. Although the predicted decrease in Bacteroidetes and increase in Firmicutes was confirmed, the team did not find a link between the altered microbial populations and aberrant energy harvesting (19, 23). More research is required to evaluate these results.

In recent years, the study of microbes that reside within the human GI tract has gained momentum. Scientists are now beginning to understand the role that the human microbiome has in mediating various physiological functions in the host. From ingested meals, intestinal microbiota catabolize carbohydrates, resistant starches, and dietary fiber, and use this plant matter as substrates for energy metabolism and other biological functions. Molecular byproducts such as SCFAs are produced from these catabolic processes. The three most prominent SCFAs found within the GI tracts of mammalian organisms are acetic, butyric, and propionic acids. These SCFAs act as ligands for receptors localized on the membranes of host epithelial cells located along the intestinal lumen and immune cells such as neutrophils. Once bound to their target receptors, these microbial byproducts initiate various physiological responses; two of the most studied are the inhibition of cancer and the reversal of inflammation within the GI tract. Current research highlights the role that intestinal microflora has in the operation of host immunity. In this section, we examine the various beneficial effects that microbial metabolites have on mammalian immunity. The new insight provided by recent research prompts investigators to question how

much of mammalian life, particularly human, is dependent upon the activity of its resident microbiome.

The microbiome is dense, and its components are numerous, especially in the human colon; overall, bacterial cells outnumber the cells of the host organism (24). These microbes contribute to maintaining the homeostatic condition of the host. This, in turn, fuels the interrelated pathways involved in the metabolism of the host. Intestinal microorganisms are instrumental in nutrient processing and absorption. For example, mice lacking conventional intestinal microflora require approximately 30% more calories to maintain a healthy body mass (18, 22, 24, 25). Sequencing of bacterial genomes such as that of *B. thetaiotaomicron* reveals that the bacteria have the capacity to break down some lipids and carbohydrates that cannot be metabolized by human cells (18, 24). Furthermore, the colonization of *B. thetaiotaomicron* in murine GI tracts induces expression of the sodium/glucose transporter, Sglt1, in murine intestinal epithelia; the transporter assists in the absorption of glucose produced by gut microflora (24, 25). Additionally, in mice, resident gut microflora assists in maintaining proper body mass indices. Colonization of germ-free mice with typical microflora leads to a 60% increase in body fat (22, 24). In addition to facilitating metabolic processes, intestinal microflora regulate immune responses of the host. Intestinal microbes produce MAMPs as byproducts of biological processes such as fermentation. One class of MAMPs, the SCFAs (acetic, butyric, and propionic acids) serve as ligands for signaling receptor(s) on host epithelial cells.

Toll-like receptors (TLRs), signaling structures located along the host epithelia, mediate host immune responses such as the recruitment of neutrophils, leukocytes, and macrophages to areas of infection and/or inflammation (20). GPR41/FFA3 and GPR43/FFA2 are expressed in immune cells and tissues of the human body, including spleen, lymph nodes, adipose tissue, bone marrow, and colon (20). SCFAs bind to these structures and initiate various physiological responses. In colon cancer cells, specific TLRs, the g-protein receptors, GPR41/FFA3 and GPR43/FFA2, regulate cell cycle death and apoptosis when bound to an SCFA, particularly propionic acid. The GPR43/FFA2 receptor accomplishes these effects through a cyclic AMP-dependent pathway via the release of caspase proteins (20). Administration of inulin-type fructans (ITFs), a type of dietary fiber, into mice transplanted with BaF-3 cells inhibits the progression of colon cancers (19). Propionic acid may function as a catalyst for this process, for it has an anti-proliferative effect on BaF-3 cells in culture and in animals. In mice, propionic acid is taken up by the liver, which partly explains its effectiveness compared to acetic acid and butyric acid. The ingestion of food substrates such as ITFs results in a change of the composition of intestinal microflora and their subsequent metabolic processes and byproducts. Colonic regulatory T-cells expressing the transcription factor Foxp3, which inhibits the proliferation of some cancers (19), are essential for limiting inflammation of the intestines, which can lead to colitis. These immune cells also rely on intestinal microbial-derived signals for proper development and function (15, 23, 26, 27). Colonic regulatory T cells (Tregs) control the intestinal balance and prevent inflammation by inhibiting the proliferation of effector T cells. For mice, microbial-derived SCFAs affect Treg proliferation and activity. In Tregs isolated from SCFA-treated, specific-pathogen-free mice, Treg Foxp3 expression is high (27). In addition to inducing the expression of transcription factors, SCFAs influence the movement (chemotaxis) of host immune cells to areas of infection. The fermentation of dietary fibers by intestinal microbes increases the concentrations of SCFAs within the intestinal lumen, thus activating the GPR43/FFA2 receptor and leading to the recruitment of defense cells by a variety of intracellular processes. In neutrophils, SCFA binding elicits GPR43/FFA2-mediated activation of mitogen-activated protein kinases (MAPKs) and protein kinase B, proteins involved in the movement of immune cells to the areas of inflammation and/or infection. Clinical data confirm this observation, as pharmacological agents that inhibit the functionality of the proteins reduce GPR43/FFA2-facilitated chemotaxis (28, 29).

Further, SCFAs affect the proliferation and functionality of host intestinal epithelial cells, lymphocytes, and macrophages through inhibition of histone deacetylation. By this mechanism, SCFAs influence the production of anti-inflammatory

cytokines and chemokines (12, 16, 26, 29). Macrophages, a source of proinflammatory agents, produce TNF-a, IL-1b, IL-6, chemokines, and nitric oxide in association with degenerative disease conditions. Once recruited to the area of inflammation via the binding of an SCFA to its receptor, macrophages engulf and kill pathogenic bacteria with the help of reactive oxygen species (ROS) and digestive enzymes. This mechanism highlights the capacity of SCFAs to regulate ROS production and to enhance the effectiveness and efficiency of phagocytosis by host macrophages. SCFAs also have the capacity to modulate lymphocytes, which are involved in host adaptive immunity, by inhibiting T-cell proliferation and the production of the cytokines, interleukin-2 and interferon-gamma. SCFAs also affect host gene expression by inhibiting histone deacetylase (HDAC), thereby increasing the acetylation of histones and other proteins, including NF-kB, MyoD, and p53 (13, 21, 28, 30-32). This is confirmed by results from other studies, one of which shows that pigs fed a diet rich in resistant starches express gene products at a higher rate than controls not supplemented with these starches. Inhibition of HDAC activity by SCFAs produced from fermentation of resistant starches by intestinal microflora contribute to the difference in gene expression. The study also expounded on the role of microbially derived SCFAs in the protection against mucosal oxidative stress, the strengthening of the colonic defense barrier, their anti-inflammatory properties, their prevention of colonic carcinogenesis, and their signaling and satiety regulation (10, 11, 14, 17, 33, 34). Thus, for higher-order mammals, including humans, the resident microbiota have an influence in regulating the internal balance and homeostasis. In sum, in the human body, the metabolic byproducts of the gut microbiome facilitate various physiological responses. The interconnectedness of bacteria and humans has been established, and this has opened an avenue for research into the utilization of these microbes for the reversal of various degenerative conditions.

5. MICROBIOME DYSBIOSIS AND DISEASE PATHOGENICITY

The human microbiome is composed of bacteria, archaea, viruses, and eukaryotic microbes that reside in and on our bodies. These microorganisms directly and indirectly mediate many of the host's physiological functions, which include facilitation of metabolic pathways and training the immune system to protect against pathogens. They also affect human physiology, both in health and in disease (35). Many of the microbe-associated diseases are not confined to the action of just 'one microbe.' Perturbations of gut microbiota can be caused by single strains of bacteria and/or an imbalance of the community structure (dysbiosis) (34). Dysbiosis is exemplified in inflammatory bowel disease (IBD), for which the bacterial composition typically shifts to a community that contains fewer Bacteroidetes and Firmicutes, and more from the phylas Actinobacteria and Proteobacteria (36). As we learn more about how microbiota influence the health of the host, it becomes evident that dysbiosis may be a cause of disease. Further, a diseased state can lead to changes within the microbiota through various mechanisms, including changes in eating habits and bowel function as well as through the application of medications such as antibiotics (35).

5.1. Crohn's disease (CD)

Crohn's Disease (CD) is an IBD of complex etiology. However, dysbiosis of the gut microbiota has been implicated in the chronic, immune-mediated inflammation associated with CD (37). This is in line with studies of ileal ICD, in which patients present with lower microbial diversity and a community structure deviating from that of a healthy gut (38, 39). Nevertheless, evidence from dietary interventions, including antibiotics, prebiotics, and probiotics, indicates that microbial imbalance can be modified and reversed (40). Although most human host-microbe associations are beneficial, several studies using culture-dependent and molecular approaches suggest that there is a dysbiosis in the gut microbiota of patients with CD as compared to those of healthy subjects (17-22). Results from studies investigating the role of RagB/Sus in the etiology of CD suggest that a closer examination is needed; other data reveal that there is a shift from a healthy microbiota towards a microbial consortium that can elicit inflammatory immune responses (37). These findings support the hypothesis that CD is manifested, in genetically susceptible individuals, by

an aberrant mucosal response to otherwise harmless bacterial antigens (41, 42). These studies need to be extended to larger research cohorts, and longitudinal studies need to be performed to assess 1) how the composition and function of the gut microbiota change over time with respect to disease inflammation and 2) how the microbiota are affected by other factors, including drug therapy and surgery (37). Recent advances in DNA sequencing and proteomics allow investigations of the structure and function of the gut microbiota without the necessity for cultivation. There have been few efforts using a multi-omics approach to study the complex ecosystem in the human gut (22). Gaining the ability to combine information about the identities of microbial community members (obtained from 16S rRNA gene-based measurements), the metabolic potential (obtained from metagenome sequence data), and expression (obtained from metaproteome data) will allow simultaneous exploration of the gut microbiota at multiple molecular levels (37). A better understanding of gut microbiota was achieved by a study of identical twins with CD to determine microbial factors independent of host genetics. Fecal samples were obtained from 10 monozygotic twin pairs with CD (discordant *n*=6 and concordant, which is inheriting the same genetic characteristic, such as susceptibility to a disease, *n*=4) and 8 healthy twin pairs. The healthy individuals had a higher bacterial diversity compared to individuals with CD. The healthy twins had similar fecal microbial community profiles relative to twins with CD, especially when they were discordant for the disease. Patients with ileal CD involvement had a different gut microbiota relative to healthy individuals and to those with colonic CD. Evidentiary data and results lend support to the hypothesis that CD is not a homogenous disease but instead a tissue response to various etiologic factors (43).

5.2. Colon cancer

For colorectal cancer (CRC), understanding the composition of gut bacteria is essential in finding out how CRC develops and can be treated. CRC develops in steps starting with abnormal cell proliferation producing aberrant crypt foci, which results in the growth of adenomatous polyps, which are precursors of CRC (44). If not found by means of colonoscopy or sigmoidoscopy and subsequently removed, adenomatous polyps, which account for approximately 70% of colon polyps, can develop into CRCs (45). CRC development from normal epithelial cells requires factors that are of genetic and inflammatory-immunological origin. These elements often facilitate the development of a tumorigenic environment. The loss of tumor suppressor genes such as *APC* (*adenomatous polyposis coli*), which is part of the Wnt/β-catenin pathway, can result in loss of control of cell proliferation and lead to the development of hyperplasia and polyps. Further, mutations in genes that encode the machinery for DNA repair, such as *hMSH2*, can contribute to colorectal tumorigenesis. Activation of immune signaling pathways by bacterial stimuli results in a loss of homeostasis that drives a proneoplastic inflammatory environment (46). Diet and lifestyle are associated with development of colorectal adenomas and CRCs. Diets high in fat, alcohol, and red meat, and low in fiber are associated with increased risk of adenomas and CRCs (47). Additionally, microbial dysbiosis is an etiologic factor for colorectal adenomas and CRCs (48). Use of molecular fingerprinting and clone sequencing to characterize the bacterial composition in normal rectal mucosal biopsies reveals that the gut bacterial composition of subjects with adenomas differs from that of control subjects without adenomas (49). Shifts in the gut microbiota can alter microbial relationships and affect host internal homeostasis. This dysbiosis is characterized by a decreased prevalence of beneficial commensals/symbionts, overexpression of pathogenic microbiota (i.e., genotoxic bacteria), invasive and inflammatory microbiota, procarcinogenic bacteria, and cancer-enhancing bacterial antigens and metabolites. These physiological events often give rise to chronic inflammation that leads to the development of adenomas, which are precursors adenocarcinomas (50).

Microbiome changes associated with specific bacteria can lead to the development of CRCs. An overabundance of *Fusobacterium* spp., a common feature of CRCs, may contribute to progression from adenomas to cancers (51). The bacterium *Streptococcus gallolyticus* may facilitate neoplastic transformation (a causative factor of

inflammation and tumorigenesis) in the colon via invasion through a breach in the epithelial barrier (52). Tumor-prone mice co-colonized with *Escherichia coli* (expressing colibactin) and enterotoxigenic *Bacillus fragilis* showed faster tumor onset and higher mortality rates due to the activity of these bacteria. The pathogenicity of both bacterial strains resulted in increased interleukin-17 in the colon and DNA damage in colonic epithelial cells as compared to mice with either bacterial strain alone (53). Lesions within the intestinal mucosa often serve as a gateway for harmful bacteria to enter into host circulation. Further, there appears to be a correlation between the adverse effects of some bacteria (e.g., *S. gallolyticus*) and colorectal tumors (54).

5.3. Bacteria as etiological agents of irritable bowel syndrome (IBS)

For individual cases of IBD, the levels of beneficial bacteria, such as *Lactobacillus* spp. and *Bifidobacterium* spp., are lower, higher, or unchanged relative to controls. Conversely, for IBS, the levels of pathogenic bacteria such as *Streptococcus* spp. (associated with increased IL-6 levels and stimulation of an immune response) and members of the *Ruminococcus* spp. (such as phylotypes of *Clostridium Group XIVa* related to *R. gnavus* and *R. torques* (mucin degraders)) are elevated (55). An investigation of fecal samples taken from test subjects showed a difference in the prevalence of the *Clostridium coccoides* subgroup and the *Bifidobacterium catenulatum* group between IBS patients and controls. The intestinal pathogens typically associated with IBS (i.e., *Helicobacter* spp. and *Clostridium difficile*) were oddly absent, whereas one case of *Campylobacter jejuni* was identified via sequencing (56). No differences in the culturable fecal numbers of Bacteroides, Bifidobacteria, spore-forming bacteria, lactobacilli, enterococci, and yeasts were evident between IBS patients and control groups. In contrast, the numbers of coliforms and aerobic bacteria were higher in the samples from IBS patients as compared to the control group (57). Analysis of entire fecal and intestinal microbial populations via the use of advanced molecular biotechniques, such as denaturing gradient gel electrophoresis (DGGE) and q-PCR, reveals that the bands produced for IBS patients and healthy subjects were consistently different. The specificity of the bands showed the presence of the bacterial genus Pseudomonas, of which *P. aeruginosa* was the predominant species, in small intestinal and fecal samples from IBS patients (58).

5.4. *Clostridium difficile* infection (CDI)

Clostridium difficile (CD), a Gram-positive, anaerobic, spore-forming bacterium first isolated from the feces of healthy infants (59), causes swelling and irritation of the large intestine and colon. CD, one of the first diseases to be recognized as microbiome-related, develops from changes to the gut microbiota and is treated by microbiota-based therapy (60). The concept that the endogenous gut microbiota mediate some form of resistance against colonization by bacterial pathogens was proposed long before CD was linked with antibiotic-associated pseudomembranous colitis (61). Infection of animals with enteric bacterial pathogens often requires pre-exposure to antibiotics. A hamster model of CD was initially used to study interactions among CD, microbiota, and host tissues (62); however, mouse models are now increasingly used. Additionally, effects of antibiotics on the mouse gut microbiome have been described, allowing researchers to investigate how specific members of the microbiome mediate resistance to colonization (63, 64). Studies with animals and humans demonstrate that antibiotics have profound and, in some cases, long-lasting effects on the structure of the gut microbiota (63, 65). Antibiotics affect the overall size of the gut bacterial community and the composition of the community by altering proportions of specific bacterial species. However, these do not necessarily occur together (66). These effects on community structure are presumed to alter the functioning of the community (67) and might reduce resistance to CDI. A meta-analysis was used to review the use of fecal microbiota transplantation (FMT) for the prevention of recurrent CDI. The analysis identified 11 studies with 273 patients through 2012. The overall efficacy of transplantation was about 90%, and there were no substantial FMT-related adverse events (68). FMT for CDI patients changes the previous microbiota to match the donor microbiota. Of the patients, 95% were cured. Further study of this phenomenon will provide an understanding of how the microbial

communities suppress CDIs (69). It is necessary to understand how these communities suppress *C. difficile* invasion and how the implantation of new communities affects other aspects of human health. Intestinal microbiota are linked with diabetes, colon cancer, obesity, and atherosclerosis. Continued research into the roles of the intestinal microbiome in health and disease are expected to lead to ways to manipulate this community for benefit while minimizing unintended harmful consequences.

6. THE DIETARY COMPOUND RES BENEFITS HEALTH AND FIGHTS INVASIVE BACTERIA AND CANCER

RES is present in grapes, peanuts, and berries and in plants after mechanical injury, fungal infection, or exposure to ultra-violet radiation (70). Japanese knotweed, *Polygonum cuspidatum*, produces the large amounts of RES (71, 72). RES is also present in various wines, especially red wine, in high concentrations (0.1–14.3 mg/l). In fact, many have credited the moderate consumption of red wine with decreased risk of coronary heart disease and some cancers (73-77). RES has various anti-cancer properties that are facilitated through changes in apoptotic signaling, metabolic pathways, other signaling pathways that regulate apoptosis, cell cycle progression, inflammation, proliferation, metastasis, and angiogenesis (27, 28). Apoptosis is triggered intrinsically or extrinsically, depending on the type of apoptotic signal (78-82). RES is effective for treatment of tumors in severe combined immunodeficient (SCID) mice. It reduces the incidence of lung metastasis, suppresses tumor growth via the regulation of microRNA-21 (*miR-21*), and inhibits cancer by reducing cell proliferation and metastasis and inducing apoptosis (83).

6.1. RES inhibits invasive pathogenic bacteria and protects resident microbes, thus promoting overall health

RES ameliorates the effects of harmful invasive bacteria (e.g., *E. coli* and *Staphylococcus aureus*). Antimicrobials of plant origin downregulate the aberrant expression of molecules that reduce host immunity (84). For test subjects, the use of plant-derived antimicrobials increases the effectiveness of antibiotics and leads to lower incidences of microbial resistance and toxicity. For instance, various flavonoids and plant antioxidants, including RES, are effective against bacteria and fungi. RES inhibits the virulence factor of *Helicobacter pylori*, a bacterium that is present in more than 80% of gastric ulcers and the etiologic agent for gastritis, peptic ulcers, gastroduodenal disorders, and gastric adenocarcinomas (85). *H. pylori*, which affects an estimated 50% of the earth's population, causes disease in hosts through expression of cytotoxic genes and through secretion of urease, which produces an alkaline environment in which the microbe persists in the presence of a normally acidic environment. As shown by disk diffusion assays, which measure the minimum inhibitory concentrations of antimicrobial compounds, RES inhibits, to variable extents, the proliferation of three strains of *H. pylori*. However, RES lowers urease activity of all three strains in a concentration-dependent manner (85, 86). For the mycobacterium *Proteus mirabilis,* RES prevents its swarming and expression of a virulence factor. It manifests pathogenicity by proliferating in great numbers and then, through various cell-to-cell contacts, induces expression of virulence factors that are regulated by RsbA. Although more research is required, the results indicate that RES positively affects the endogenous microbiome of the host, thereby producing beneficial protective effects (15).

6.2. RES inhibits cancer cells through modulation of onco- and tumor-suppressor genes

RES regulates the expression of both pro-cancer and tumor suppressor genes, including that for the transcription factor STAT3, which controls genes associated with cancer progression and proliferation. STAT3 increases the methylation of CpG islands of tumor suppressor genes by regulating the expression of DNA methyltransferase 1, which facilitates genetic methylation, and by interacting with the enzyme (12). Inflammatory conditions within the body can foster an environment conducive to the development of malignant tumors. Cell signaling molecules such as pro-inflammatory cytokines and chemokines, found in a variety of cancers, are associated with the tumor microenvironment. Nuclear

factor κb (NF-κB), a ubiquitous signaling molecule associated with various immune responses and pathways within the body, including the response to inflammation, is involved in the development of various cancers. NF-κB is associated with various other cyto/chemokines. STAT3 shares commonalities with NF-κB, including their concurrent upregulation during the development of cancers and their role as nuclear transcription factors regulating the expression of genes involved in the progression of tumors (16). STAT proteins are inter-related with NF-κB, and the proteins often co-regulate oncogenic and tumor suppressor genes. STAT3 transcription levels are commonly elevated in breast, prostate, and head/neck cancers and in various hematologic malignancies. In some scenarios, acetylated STAT3 acts as an upstream regulator of NF-κB. The protein facilitates the processing of *p100* to *p52*, which activates NF-κB (17). An immune system with the capacity to respond to and thereby mediate inflammation is necessary for suppressing the development of cancers. STAT3 is involved in the inhibition of mammalian anti-tumor immunity. The mechanisms by which this protein exerts tumor-promoting effects have been documented. STAT3 antagonizes the anti-tumor activity of NF-κB-facilitated expression of anti-tumor signaling molecules such as the T helper 1 (TH1) cytokine, interleukin 12 (IL-12), and interferon- ɣ (IFN ɣ). Such molecules are necessary for the functioning of both T-cell mediated and innate immunity. The signaling of such molecules by antigen-presenting cells is required for the proper functioning of immune cells. Immunosuppressive and tumor-promoting effects of immune cells, including myeloid-derived suppressor cells and tumor-associated macrophages, are enhanced by STAT3 signaling (11, 13, 14, 16, 21). The development and activity of immune cells that promote the growth of malignant tumors, particularly TH17 T-cells and regulatory T-cells, are regulated in part by STAT3. Thus, STAT3 is involved in the expression of cytokines and growth factors that, in turn, upregulate the expression of associated cellular receptors. As a result, STAT3 is a link in the loop between adverse immune cell activity and development of the tumor microenvironment. STAT proteins, particularly STAT3, facilitate inflammation, which is conducive to tumor progression and proliferation. Additionally, the proteins suppress normal anti-tumor immunity. Therefore, these proteins are a target of interest for the development of effective alternative treatments for cancer (13, 16, 19, 21, 23).

STAT3, when acetylated and activated, induces epigenetic effects, namely the silencing of tumor suppressor genes by DNA methylation and chromatin modulation. Thus, STAT3, like the closely associated NF-κB, is upregulated in a wide range of cancers. STAT3 activation leads to the constitutive expression of oncogenes. RES, in addition to its other beneficial properties, downregulates the expression of STAT3. RES, an inhibitor of genetic acetylation, has the capacity to reverse aberrant CpG methylation of the promoter regions of tumor suppressor genes. RES also inhibits STAT3 acetylation and thereby its genetic expression. This, in turn, leads to the remodeling of chromatin and access by transcription factors to tumor suppressor or anti-cancer genes due to the relaxed state of the DNA molecule. The actions of oncogenic genes/transcription factors are reversed in anti-cancer responses. In addition to molecules such as STAT3, oncogenes such as estrogen receptor alpha (*ERα*), which is associated with a poor prognosis for survivability when expressed in malignant tumors such as melanomas and certain types of breast cancers, are also regulated by RES. RES affects *ERα* expression through modulation of histone deacetylase (HDAC) activity (26, 34). HDAC inhibitors, such as RES, induce the hyperacetylation of oncogenic transcription factors such as STAT3 and NF-KB. The epigenetic acetylation of these factors increases their oncogenic activity and results in tumor proliferation and progression. Therefore, inhibition of HDAC activity by RES leads to tumor regression (25, 33).

Additional studies have been conducted in regard to the inhibition of various cancers by RES through the mediation and regulation of proto-oncogenes and tumor suppressor genes. One such study concerned the mechanisms of progression and proliferation of colorectal cancer (CRC), the third most common cause of cancer deaths in the United States, affecting men and women equally (87). For CRCs, a commonly identified abnormality relates to the functionality of the tumor suppressor gene, *adenomatous polyposis coli* (*APC*), a regulator of the

Wnt pathway, which is implicated in the development of numerous types of cancer. This pathway is responsible for maintaining cellular homeostasis and the pool of pluripotent stem cells that differentiate into various types of cells to constitute the different tissues/organs of the body (27). *APC* executes this via the degradation of β-catenin, a transcriptional activator responsible for the activation and transcription of Wnt genes. Loss of proper *APC* function leads to the cell's inability to degrade β-catenin, resulting in its stabilization and relocation to the nucleus, where it induces transcription. Activation of the Wnt pathway typically leads to the accumulation of undifferentiated cells that form an adenoma, which can develop into a malignant tumor (27, 29). For this to occur, however, more molecular events are needed. These include transcription or upregulation of the *Kras* oncogene, which is associated with chemoresistance and tumor metastasis and with poor patient survival. *Kras* mutations can alter signaling pathways, such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K), which are involved with the development of a variety of cancers. *Kras* also acts in concert with the loss of *APC* to enhance activation of the Wnt pathway, leading to an aggressive CRC phenotype that is difficult to treat (24, 30, 31). For colon cancer cells, RES induces apoptosis, inhibits cell proliferation, and kills cells in culture. RES also inhibits the growth of CRCs in mice, and it suppresses tumor formation in the colons of genetically altered mice that are predisposed to development of tumors within the GI tract. RES regulates the expression of certain genes via post-transcriptional epigenetic modifications. In human lung cancer cells, RES suppresses the expression of *Kras*, a finding consistent with other reports showing that RES inhibits the expression of *Kras* in other cancer cells and in experimental animals (31). Feeding mice a diet supplemented with RES (210 mg/day) reduced the expression of *Kras*, prevented tumor development, and caused the regression of established tumors. In addition to these promising results, there was little or no toxicity of RES; the compound was well tolerated and was deemed safe. Molecular analysis revealed that RES induced the transcription of microRNAs that regulate expression of *Kras*. The microRNA, *mir-96*, inhibits *Kras*-dependent tumor formation by preventing the translation of *Kras* mRNA. *Mir-96,* similar to the action of other small non-coding RNAs, hybridizes to the 3'-untranslated region of the mRNA and disrupts the access and processivity of the ribosome. This microRNA is elevated in both tumor and non-tumor tissues of mice treated with RES. For cancers in an advanced state, *mir-96* is downregulated, and *Kras* is simultaneously upregulated. The reverse is true for cancers that are regressing after treatment with RES. Thus, RES inhibit cancers via the epigenetic upregulation of *mir-96*, which inhibits expression of the oncogenic *Kras* (38, 40-42, 88).

7. HEAT SHOCK PROTEINS (HSPS)

Heat shock proteins (HSPs) were discovered in 1962 following a laboratory mistake in which the temperature of an incubator where *Drosophila melanogaster* larvae were kept was accidentally elevated, which resulted in new puffing patterns of the polytene chromosomes in salivary glands (59). Since their discovery, the functions of HSPs in response to various stressful stimuli, including human cancer and cystic fibrosis, have been documented (17-19). Therefore, HSPs have made an impact in various areas of research, including the medical and biological fields, because of their diverse functions in both pathological and normal conditions (20, 21). HSPs consist of molecular chaperones of approximately 70kDa that are involved in protein homeostasis (89). Molecular chaperones, which are found in all living cells and form part of the defense system against internal and external stressors, are grouped into two major categories according to their amino acid composition, molecular weight, and cellular function (22, 23). These proteins belong to the small HSP family, including Hsp27, or to the larger 70 kDa HSP family, including Hsp70, Hsp60, Hsp90, and Hsp110. The high-molecular-weight HSPs, which range from 60 to 110 kDa, are ATP-dependent. Their primary cellular functions are binding to and folding of nascent proteins through ATP-dependent allosteric organization; assembling and transportation of proteins across membranes, and degradation of improperly folded peptides (24, 25). Small-molecular-weight HSPs, or Hspβs, which range from 15 to 43 kDa, are ATP-independent molecular chaperones; they function in embryo developmental processes,

such as the formation of respiratory organs and cardiac muscles. Additionally, they serve as biomarkers for tumor formation, and they mediate protein folding (15, 23, 27).

7.1. The role of HSPs in mediating cellular homeostasis

The human Hsp family consists of eight members. Some of these have organelle-specific localizations and tissue-specific expression, but several members have overlapping cellular functions (10-12). Only three of the eight show stress-inducible expression; Hsp70 is one of these. Under normal circumstances, Hsp70 acts as a molecular chaperone, assisting the process of protein folding; however, for cells under stress, Hsp70 expression increases and its behavior changes. These highly-conserved proteins are recognized for their diverse functions, including protein folding, translocation of proteins across membranes, assembling and disassembling of proteins, signaling transduction, degradation of misfolded proteins, and mitochondrial generation of reactive oxygen species (ROS) that can induce apoptosis (80). They also protect nascently translated proteins, reduce proteotoxic protein aggregates, and serve general housekeeping roles in maintaining protein homeostasis. They enhance cell survival in response to stressors such as elevated temperature, hypoxia, and oxidative stress. These responses provide cellular protection against protein denaturation and possible degradation of misfolded proteins, which, in turn, result in protein aggregation and possibly cancers (14).

7.2. SCFAs and RES prevent HSP activity and induce apoptosis

As apoptosis, often triggered by cytotoxic drugs, begins, two signaling pathways trigger caspase enzymes that cleave various substrates, including those of the mitochondrial membrane, leading to cell death (90). Generally, there are two pathways of apoptosis or programmed cell death; cells undergo apoptosis through either an intrinsic or an extrinsic pathway. The intrinsic pathway involves intracellular cues or harmful stimuli of some sort (e.g., DNA damage, ischemia, or oxidative stress), stimulating the release of the apoptogenic molecule, cytochrome c, from the mitochondria. The extrinsic pathway involves the stimulation of cellular death receptors belonging to the tumor necrosis factor (TNF) receptor family and located on the cellular membrane. This typically leads to a cascade of events that end in activation of the receptor-proximal caspase-8 or caspase-10 within the death-inducing signaling complex (91, 92). HSPs prevent apoptosis by interfering with caspase activation and activity. The overexpression of Hsp70 inhibits caspase-mediated proteolytic activity, which results in an irreversible commitment of cells to apoptosis in response to various cellular stressors, including the accumulation of misfolded proteins, ROS, and DNA damage (93). Atypically low levels of intracellular Hsp70 can, in some instances, initiate apoptosis through the activation of caspase-3 in the absence of any stressful stimuli (94). At the post-mitochondrial level, Hsp70 inhibits apoptosis downstream of the release of cytochrome c and upstream of the activation of caspase-3. This anti-apoptotic effect is explained by the Hsp70-mediated modulation of the apoptosome. Indeed, Hsp70 binds to apoptotic protease activating factor 1 at its ATPase domain, thereby preventing the recruitment of procaspase-9 to the apoptosome (95). HSPs block both the intrinsic and the extrinsic apoptotic pathways through the interaction with proteins at three levels: (1) upstream of the mitochondria, thereby modulating signaling pathways; (2) directly at the mitochondrial level, thereby controlling the release of cytochrome c; (3) and at the post-mitochondrial level (96). Thus, HSPs facilitate cancer cell survival in response to various stressors. RES and diet composition affect the expression of Hsp70. RES downregulates the expression of Hsp70 at the mRNA and protein levels. RES lowers Hsp70 protein expression in K562 cells (a human myelogenous leukemia cell line) by as much as 90% in a dose and time-dependent manner. Additionally, RES lowers HSF-1 (the transcription factor that regulates the expression and synthesis of Hsp70) transcriptional activity (97). In cell cultures, SCFAs, in particular butyric acid, induce the expression of several HSPs, including Hsp70 (96). However, tests with mice show that plant derivatives affect HSP levels within the gut (98), and, with rats, plant lectins reduce the levels of Hsp70 in the jejunum (98). Thus, there is a relationship between

the consumption of plant-based foods, gut microbial activity, and the cytoprotective effects produced by microbes. Hsp70 increases cell survival and is a factor in cancer proliferation. Intestinal microbes use the cellulose and digestion-resistant fibers in plant tissues as substrates to produce SCFAs, which induce apoptosis in affected cells, thereby preventing cancer development and tumor growth via the inhibition of HSP activity (98).

8. CONCLUSION AND FUTURE PERSPECTIVES

This report highlights the capacity of a natural dietary compound, RES, and metabolites produced by intestinal microbes (SCFAs) to elicit beneficial and protective physiological effects. The capacity of RES to affect endogenous microbial activity in relation to health and the inhibition/regression of disease is relevant in dealing with chronic debilitating conditions such as cancer. This discourse emphasizes how microbes are directly and indirectly (via the production of metabolic byproducts) linked to the proper biological functioning of a host organism, and how RES can affect biochemical pathways and the life, prevalence, and virulence of microbes. Furthermore, these compounds modulate the efficacy of HSPs and induce apoptosis of cancer cells. RES can be derived from various plant sources, and intestinal microbiota use plant fibers to produce protective metabolic byproducts, SCFAs. These seemingly related phenomena establish a link between diet composition, endogenous microbial activity, reduced cancer risks, and overall health -- a topic that should be explored further.

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Abbreviations: (*APC)* Adenomatous polyposis coli gene, (CD) Clostridium difficile, (CD) Crohn's Disease, (CDC) Centers for Disease Control and Prevention, (CDI) Clostridium difficile infection, (CpG) Cytosine phosphate guanine group, (CRC) Colorectal cancer, (DGGE) Denaturing gradient gel electrophoresis, (*ERα*) Estrogen receptor alpha gene, (FMT) Fecal microbiota transplantation, (GI) Gastrointestinal tract, (GPR41/FFA3) G-protein-coupled receptor 41 or free fatty acid receptor 3, (GPR43/FFA2) G-protein-coupled receptor 43 or free fatty acid receptor 2, (HDAC) Histone deacetylase, (*hMSH2)* Human MutS-homolog tumor suppressor gene, (HSF-1) Heat shock factor-1, (HSPs) Heat shock proteins,

(Hspβs) Heat shock protein β-1, (IBD) Inflammatory bowel disease, (IBS) Irritable bowel syndrome, (IFN ɣ) Interferon- ɣ, (IL-12) Interleukin 12, (IL-1b) Interleukin 1 beta, (IL-6) Interleukin 6, (ITFs) Inulin-type fructans, (K562) Human myelogenous leukemia cell line, (kDa) Kilodalton, *(Kras)* K-Ras oncogene, (MAMPs) Microbe-associated molecular patterns, (MAPKs) Mitogen-activated protein kinases, (*miR-21*) microRNA-21, (*mir-96)* microRNA-96, (MyoD) Myogenic Differentiation 1, (NCHS) National Center for Health Statistics, (NCI) National Cancer Institute, (NF-kB) Nuclear factor kappa B, (NF-κB) Nuclear factor κB, (*NLRP6*) NLR Family Pyrin Domain Containing 6 gene, (*Nod2*) Nucleotide Binding Oligomerization Domain Containing 2 gene, (PI3K) Phosphatidylinositol 3-kinase, (q-PCR) Quantitative PCR, (RES) Resveratrol, (ROS) Reactive oxygen species, (RsbA) Regulator of swarming behavior, (SCFAs) Short-chain fatty acids, (SCID) Severe combined immuno-deficient, (STAT/STAT3) Signal transducer and activator of transcription, (TH1) T helper 1, (TH17) T helper 17, (TLRs) Toll-like receptors, (TNF) Tumor necrosis factor , (TNF-a) Tumor Necrosis Factor alpha, (Tregs) Regulatory T cells and (Wnt) Wingless-related integration site

Key Words: Resveratrol, RES, short-chain fatty acids, SCFAs, Heat Shock Proteins, HSPs, Cancer, Microbiome, Microbiota, Review

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