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Simulate the Dynamic Interactions Across Nutritional Supplements, the Polybiome, and the Biochemical Approach Dependent on Patient-Derived Gastrointestinal Knowledge

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ABSTRACT

Dietary and lifestyle planning decisions, dysbiosis in the composition of the microbial community and the production of bioactive metabolites by the gastrointestinal microbiota are all factors that have a significant influence on the mucosal integrity of the intestines and the progression of diseases like colon cancer. Even though intestinal microorganisms or its metabolites that generate play key roles in a wide range of biochemical processes, scientific exploration into the connections between dietary supplements and the composition of the host's intestinal microbiota has been limited so far. Therefore, colonic patients derived from gastrointestinal tissues have made it possible to design in mammalian cells environments with an adequate and appropriate level of intelligence to simulate both functional and pathophysiological nutrition, gut microbiome and host interactions, which is an opportunity that has never before been available. Colon patient reactions to intestinal microbiota biochemical processes and gut bacteria may give new insights into how these metabolites may mitigate or trigger illnesses. This would be a big step forward in our understanding of how the composition of the gut microbiota is influenced by nutrition, both in the host and in the host's environment.

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Introduction

There is a correlation between diets high in bioactive constituents and soluble and insoluble dietary nutrients and a decreased likelihood of developing serious illnesses [1]. A variety of plant-based foods are a popular source of bioactive components and soluble and insoluble dietary fiber. In addition to unhealthy lifestyles, metabolic syndrome, and diseases of the cardiovascular and central nervous systems, these ailments would include cancers that impact the gastrointestinal tract [2]. On the other hand, in the first place, it is challenging to draw a clear link between the native components that the plant possesses in their original condition and the biological consequences of these phytochemicals. This is due to the fact that these compounds' interactions with the surrounding environment of the plant that produces them are what create their therapeutic properties [3]. Most nutrients do not undergo any metabolic activity until they reach the stomach, where they are unaffected by the acidic environment there. As an example, the carbohydrate attached to flavonoid glucosinolates is metabolized at the brush border of the small bowel, releasing aglycone in the process and eliminating the glucoside [4-6]. This glucoside may enter epithelial cells by osmotic gradient due to its extreme hydrophilic nature and closeness to the cellular membrane [7]. The flavonoid aglycone undergo conjugation after entering the liver, which eventually results in the release of metabolites such as sulfur dioxide, glucuronic acid, and dimethyl intermediates [8]. The drug doesn't enter the bloodstream until after this process is complete. Polymeric flavonoids, for example, arrive in the colon virtually undisturbed in the great majority of instances [9]. Flavonoids and indigestible polymers are exposed to the gut microbiota in the large intestine, where they interact with it to decide their fate [10,11]. This area experiences a significant amount of microbial conversion of biomass, which results in the creation of gut microbial metabolites made from polyphenols and short chain fatty acids [12-14]. Nearby, through the modulation of the gut microbiota while also exerting their bioactivity on intestinal epithelial cells, or chronologically, after absorption, where some are conjugated in the liver and then released in the blood system to trap various organs, including the nervous system [15-18]. Because of their bioactivity, they have an effect on the intestinal epithelial cells and also influence the microorganisms that exist in the gut. The byproducts that are created by the microbes in the gut might have beneficial or harmful consequences [19]. These compounds may have a positive effect on the immediate environment by influencing the composition of the gut bacteria and enforcing their bioavailability on the cells that line the intestinal tract. Consumption of high-fat and high-calorie items, such as those often found at fast-food chains, is indicative of a sedentary lifestyle. Because of this tendency, there is an increased probability of developing a variety of diseases. This

way of eating has been linked to a higher risk of both colon cancer and inflammation of the colon [20,21]. This means that this eating behavior may result in colon cancer. For instance, the part of the small intestine absorbs bile acids when you eat a meal that is heavy in fat. This facilitates the body's emulsification of dietary lipids and absorption of fat-soluble vitamins. Elevated amounts of secondary bile acids are produced as a result of the gut bacteria's further digestion of these cholesterol-derived chemicals in the colon, which may cause colorectal cancer. Cholesterol is one of the most significant risk factors for colorectal cancer. Trimethylamine and trimethylamine N-oxide, both produced by the microbiome, have been found in high concentrations in people with colorectal cancer [22]. These metabolites are produced during the digestion of dietary choline and carnitine. Many of these metabolites have been connected to typical Western (American) diets. On the basis of voluminous data acquired from studies on colorectal cancer, the International Agency for Research on Cancer concluded that processed beef was a chemical that was carcinogenic to human. These conclusions were drawn from studies on colorectal cancer. There is a possibility that carcinogenic chemicals, such as N-nitroso agents, polychlorinated biphenyls, and chromophoric amines, would reach the colon and increase DNA adducts and DNA damage there. This is due to the fact that these compounds are most often present in the colon [23]. More research is needed to fully understand gut homeostasis, as well as how to prevent and spread illness. However, the diet and lifestyle microbiota-host picture has recently come to light as a possible way to treat inflammatory bowel diseases like colon cancer.

Metabolites Enable a Better Understanding of Specific Dietary Patterns on the Intestinal Microbiota

It is necessary to take into consideration a great number of crucial elements, such as one's food, their biome, the microbiota in their gut, bioactive components, and metabolic pathways (Figure 1). The consumption of daily calories, our polybiome, and the biochemical processes of the human gastrointestinal microbiota are some of the crucial elements that need to be properly addressed. Is it really the case that the great majority of us are nothing more than the accumulation of all of the nutrients that we intentionally put into our bodies? Even though food that is rich in nutrients is necessary for human life, it's possible that various kinds of food will have varying impacts on our health and development. [24-29].

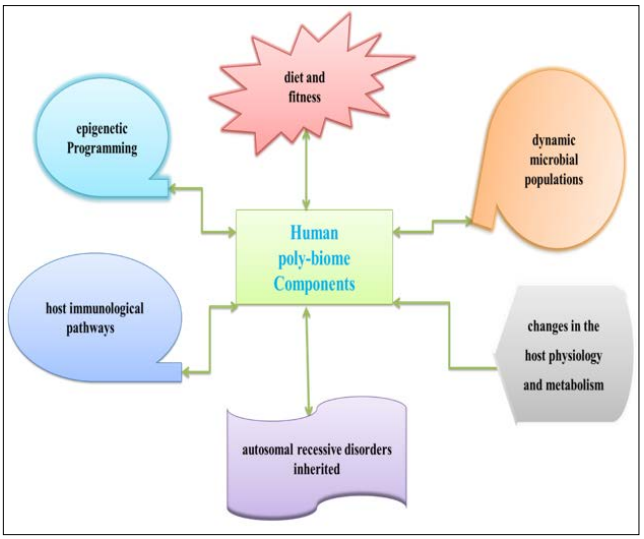

Figure 1: Metabolomics focuses specifically on the human poly-biome human's multidimensional biotic diversity

Despite the fact that diet has a substantial influence on psychological well-being, there are intricate links between microbiota composition, posttranscriptional factors, and various other socioeconomic and demographic changes necessary for cancer propagation [30]. During digestion, the digestive system breaks down nutrient-rich foods into a variety of small molecules. Some of these molecules are absorbed by the intestinal mucosa after consumption, while the remainder is processed further by the intestinal bacteria. Enzymatic hydrolysis is the term used to describe the process of breaking down these molecules into their component parts. Microbial colonies are widely known to predominate in the human digestive tract (Figure 2).

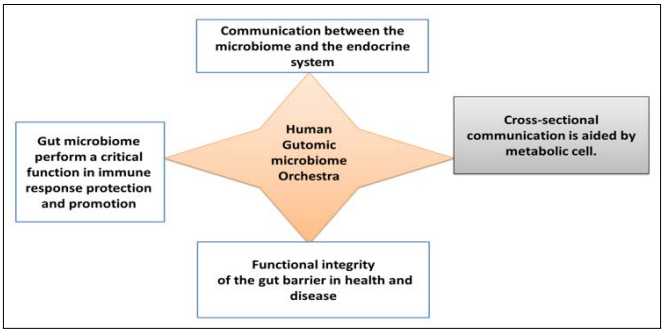

Figure 2: Immune Biochemical Framework poly-biome-Brain Multifaceted Collaborations Deciphering

In this area, there are thought to be 1,000 infectious species. Humans were predicted to have tens of thousands, if not hundreds of thousands, of distinct microbiota species in their upper and lower digestive tracts, but the number is lower in the stomach and proximal intestines than in the colon, which has at least 1011 cells/g and a substantially higher density. By modifying the chemical properties of substances that enter the body through food and medicine, microorganisms in the stomach may generate toxicological effects. Though we are starting to comprehend the complicated connection between the gut poly-biome and these pathogenic species, concerns remain concerning the roles that eating habits, endophytic microbial biodiversity in the human gut, and anabolic-neuro-biochemical networks of microbial populations in the intestines play in maintaining tissue homeostasis and physiological processes inside a bodily organ. And this is the first evidence that the microbiota in the midgut is endophytic, as De Barry (1866) stated in his description of endophytic [30-40]. Since then, the term has been entrenched in the publishing industry and is no longer limited to agricultural uses. From conception to death, people are infected with tiny parasites that our systems cannot fight because they are plants. It is a powerful and complex endophytic interaction that is influenced by a variety of psychological and extrinsic variables, the sum of which influences population welfare. European Nutritional Supplement Research Oncology is a well-known scientific discipline in the United States and other nations across the world; this is one of the largest group studies ever undertaken, and it indicated that individuals who ate more fruits, vegetables, and fiber had a lower risk of developing a variety of malignancies Figure 3.

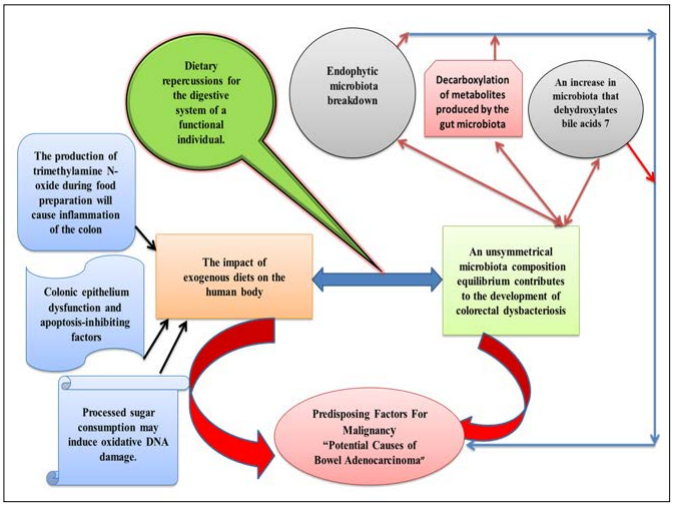

Figure 3: Focusing on Developing Between Environmental Intake and Bowel Health, Commensal Poly-Biome and Metabolic Product by Microbiota in the Gastrointestinal

Remarkably, a higher intake of dietary phytochemicals, such as bioactive components and soluble and insoluble diets, together with active substances that neutralize singlet oxygen, is related to a substantially reduced risk of gastrointestinal cancer, according to scientific evidence and research [41-44]. Concerns about the pharmacological effects of endogenous phytonutrients and genetically altered microbes nevertheless remain in large numbers. Research methods that are now being used to examine the effects of food ingredients on inflammatory disorders, bioaccumulation interactions between food components and the human body, the examination of the intestinal poly-biome, and the potential antibacterial capabilities of phytochemicals, such as phytonutrients vs. malignancy, all rely heavily on supplying natural biological molecules to a variety of mammalian species using two-dimensional carcinoma models [45-56]. The pharmacological effects of different classes of drugs cannot be assigned to their original components but must be attributed to their metabolites [57-59]. Proliferative and tumor cells cultivated in two-dimensional phospholipid bilayers atop polymers only partly mimic the crucial physiological complexity, spatial patterns, and intracellular pathways inherent in three-dimensional design [60-61]. Despite the fact that the majority of substances with a life-promoting effect and organ diseases of concern share similar findings, they are especially significant in gastrointestinal ailments for the following reasons: Understanding three features of the gut's epithelial tissue is critical: its cellular stress design, the ongoing effect of dietary metabolites on it, and the complex relationship between microbes and those progenitor cells [62-69]. To address these issues, several modalities, each with a greater level of complexity than two-dimensional digit types, have already been developed [70-75]. Even though these animals and people have comparable metabolic health, their intestinal poly-biomes are not identical, and a human-centered model often misrepresents the genuine relationships occurring in occupants [76-78]. This strategy transplants the intestinal polybiome into a host that is not physiologically compatible with it. This implies that the ecological factors that cause and propagate dysbacteriosis in persons, such as lifestyle choice, dietary habits, and disease polymorphisms, are no longer applicable to animal experiments [79-85].

Colonic Patient-Derived Colonies Show that Phytoconstituents Have a Central Role in the Development of Organogenesis and Pathogenicity

It has recently been proven that cells taken from adult tissue biopsies and resections have the ability to survive, multiply, and self-organize into three-dimensional structures in vitro that are highly comparable to the tissue of origin, employing procedures for producing colonic patient-derived cells. Three-dimensional gastro-intestinal patient-derived models have thus been demonstrated to be useful model systems in research aimed not only at decoding healthy structural and functional integrity but also at studying molecular pathways associated with illness development, enlargement, and treatment adherence [86-92]. The intestinal epithelium is a well-planned, self-renewing tissue with a proliferative crypt compartment and a differentiated villus, among other traits [93-94]. Continuous cellular turnover of the intestinal epithelium is maintained by stem cells at the bottom of crypts, which create transit-amplifying cells that later develop into numerous gut epithelial cell types, including epithelial cells, secretion, Kulchitsky cells (are a specific sort of neuropsychiatric cell that may also act as exocrine cells), and intestinal absorptive cells, among other types of the intestinal mucosa. One of the greatest approaches to researching the influence of gut microorganisms on health is to employ a model that retains in vivo cellular diversity while maintaining the main roles of the intestinal mucosa [95]. Researchers have shown that the intestinal epithelium may be examined in culture and used for food transport, nutrient sensing, and hormone secretion studies using Intestinal patient-derived mimicking mouse small intestines [96-97]. Following that, human gastro-intestinal patient-derived cells were used to model nutrient transport physiology during digestion, and mouse Intestinal patient-derived cells were used to study intestinal processes for dietary fat absorption [98-103]. Several research groups have begun to investigate various chemicals and dietary components that may either enhance or deteriorate the health of the intestinal epithelium. More research shows that several dietary factors influence the growth of Intestinal patient-derived in vitro cells [104-111]. They found that a number of dietary ingredients were unable to appreciably alter the progression of gastro-intestinal disease. The hydroxycinnamic acid known as trans-caffeate or sodium caffeate is also known as 3,4-hydroxycinnamic acid. In contrast, it inhibited patient-derived growth in a concentration-dependent manner [112]. There are fewer crypt-like structures as there is more trans-caffeine. The crypt is an enteric burial chamber in the large intestine that is part of the endocrine system. These results were similar to those of earlier in vitro studies, and they were verified in vivo [113,114]. Although certain findings, such as sodium L-glutamate and caffeoylquinic acid, were consistent with prior surveys, others were not. Based on these results, it's clear that testing phytochemicals with Intestinal patient-derived is still in its early stages [115-117]. For future research, the experimental design must take into consideration not only that the findings may give useful insights into in vivo models rather than two-dimensional patient-derived models but also that the observed responses are confined to the epithelial component of the intestinal mucosa as opposed to the whole gut [118]. Moreover, Numerous observational studies have shown statistically significant associations between eating a lot of cruciferous vegetables and a lower risk of a variety of gastrointestinal cancers [119, 120]. Chemicals such as indole-3-carbinol, which has recently been studied in small intestine rat tumor tissues, are thought to be responsible for the potential health benefits of eating brassicas or cruciferous vegetables. The results provide compelling evidence that indole-3-carbinol affects NOTCH and WNT signaling pathways, playing a critical role in the upkeep of correct cell fate and, therefore, the differentiation of goblet cells in the test tube [121,122].

3-Indolemethanol molecules may combine in the acidic environment of the stomach to generate a complex combination of polycyclic aromatic compounds known as acid condensation products, such as diindolylmethane, a phytonutrient and phytoindole found in cruciferous vegetables such as broccoli, Brussels sprouts, and other green leafy vegetables. Diindolylmethane is an antineoplastic medication, and its biological activity may differ from that of indole-3-carbinol [123]. However, due to the action of thioglucoside glucohydrolase, also known as myrosinase in colonic bacteria, the synthesis of indole-3-carbinol in the large intestine may continue to occur during the transit of glucosinolates (GSLs), a category of unique bioactive metabolites, also identified (S-glucopyranosyl thiohydroximates), albeit to a lesser extent. Therefore, it is possible that the little amount of indole-3-carbinol that is anticipated to reach the gut will have little impact on the NOTCH and WNT signaling pathways. In the absence of animal models, this static and multicellular system may be a suitable alternative to animal models for the prescreening of gut microbial metabolites. But before they are published, any big findings need to be tested on animals. Researchers now have new opportunities to investigate the role of diet in carcinogenesis because of the use of colonic patient-derived made from malignant colorectal lesions [125,126]. This includes looking at how food affects intestinal epithelial homeostasis. They have recently been proven to have a significant chemoprotective influence on human colorectal cancer by investigating colon-tissue patient derived as a preclinical model system. The two most reliable ways in which flavones prevented the production and expansion of APC generated from the gastrointestinal tract were by inhibiting the cell cycle and triggering programmed cell death. Colon cancer is defined by the unstudied clinical and pathological features of numerous colon cancer tumoroids, Mini from Adenomatous Polyposis Coli, and Multiple Intestinal Neoplasia -transgenic mice [127]. On a molecular level, gene expression analysis demonstrated that flavone treatment inhibited prosurvival and consciousness pathways, particularly Hippo signaling, in patient-derived cells. Even if these results are encouraging in terms of nutrition, polyphenol type-A pro-anthocyanidins are subject to significant metabolism after they have entered the gastrointestinal system. These molecules may pass through the distal large intestine unharmed. Once there, the bacteria in the human stomach swiftly convert them into low-molecular-weight polyphenols. and omitted as a consequence, when flavan-3-ol monomers (catechin and pro-anthocyanidins), dimers, and trimers reach the colon, the gut bacteria may utilize them. Furthermore, when Choy and his colleagues studied the feces of pigs given polymeric pro-anthocyanidins, they reported that only 10% of the polymeric pro-anthocyanidins had been identified [128-135]. When pro-anthocyanidins are broken down, it has been demonstrated that they have a positive influence on the development of cancers [136-141]. An anti-inflammatory drug is made by combining polyphenolic compounds with Curcuma longa [142-145]. Curcuma longa, or turmeric which was originally studied on colonic carcinoma cell lines to determine whether the combination may help lower mortality and morbidity. It was shown that taking anthocyanins and capsicum supplements reduced the transcriptional activity of the tumor-promoting oncogene, CCND1 (Cyclin D1). It has also been found that the enzyme phosphatidylinositol 3-kinase 3B (PDE3B) plays a key role in cytokines such as tumor necrosis protein kinase proliferator-co-expression [146]. PDE3B is a chromosome that is linked to the co-expression of phosphoinositide proliferators. It is also in charge of certain maturation and impedance mismatch up- and down-regulation in both basal insulin signal transduction pathways [146]. The development of submucosal patient-derived cancer cell glioblastoma that had been produced from adult male HCT116 (ATCC® CCL-247TM) tissue was examined in conjunction with capsaicin and anthocyanidins in the same embedding animal model. The goal of this research was to see whether c57BL/6 mice might be prevented from spreading by integration. Anthocyanins, including CCND1 (Cyclophilin D1) and phosphodiesterase 3B, were able to successfully diminish the knock of expression when administered alone. This is a really curious observation [147-150]. Alternatively, mouse microbome metabolic processes have a greater impact on the release of gut microbial metabolites than anthocyanins do on regulating these responses. However, the combination of turmeric and pro-anthocyanidins prevented tumor formation in vivo to a greater extent than turmeric or pro-anthocyanidins used as single agents did for CCND1 (Cyclin D1) and phosphodiesterase 3B expression [151, 152]. Last but not least, the scientists created biomaterials that were once again derived from the lesions of patient populations and contained organoids with tumor-like characteristics. The word "tumoroid" has been thought to imply the concept of tumor-like organoids. Tumoroids are mostly derived from different polyps composed of adjuvant restorative long-suffering populations and have the capacity to mimic the conventional malignant tumor vasculature. Tumoroids created from patients' malignancies that include tumor growth are divided into four platforms; behind each lies a more detailed division including specific information on the nature of the tumor and how it affects the rest of the body. Tumoroids are now recognized as a very valuable resource for doing low-cost research on potential anticancer medications that may be employed in pharmacogenomics. These platforms are usually denoted by roman numerals, and samples were taken from the patient from platform zero, which is the platform when the tumor is in place and has no extent, to platform IIA, which is the platform migration of tumor cells to neighboring tissues, known as metastasis https://www.cancer.org/treatment/understanding-your-diagnosis/staging.html, to corroborate the tendencies seen in 2-dimensional a549 cells and study that examined living animals Curcumin and pro-anthocyanidins work together to suppress the expression of genes that code for phosphodiesterase-3B (PDE3B) and CCND-1 (Cyclin D1) [153]. However, treatment of colon tumoroids with natural pro-anthocyanidins alone had no effect on the methylation state of CCND-1 (Cyclin D1) or Phosphodiesterase-3B [151]. Numerous studies on phytonutrients and their effects on patient-based gastro-intestinal induced pluripotent stem cells that mimic homeostatic systems and malignancy development have been conducted so far. To our knowledge, however, tumor initiation and propagation through diet-related metabolites, as well as the preventative potential effects on gut microbiome metabolic pathways in the presence or absence of carcinogenic chemicals, have not been thoroughly investigated [154]. Overall, patient-derived gastro-intestinal induced pluripotent stem cells obtained from healthy or diseased tissue provide a beneficial tool for investigating the influence of dietary patterns and variables on cellular function [155]. Despite the fact that this technology is an important tool for understanding various pathological processes that affect individuals and, as a consequence, helps us identify new methods of preventing and treating illness, the importance of planning experiments with nutrients, metabolic activities of natural food components, and substances that enter the small intestinal mucosa in mind cannot be overstated

[156,157]. In an ideal scenario, one would look at the behaviors of both physically active and degenerative disease patients. This should have been considered in studies aiming to mimic systemic absorption by adjusting the brush border membrane lining of the small intestine or endothelial exposures by manipulating the apex of the epithelial cell membrane. It will depend on how much the bowel asymmetry is altered adversely [158].

Analyzing the Biological Modifications Caused by the Microbial Diversity at the Intestinal Mucosa

In contemporary microbial genome sequencing, dynamic meta-omic techniques are increasingly being utilized to investigate microbiological interactions rather than just polybiome assemblages. This is in contrast to the traditional approach, which focuses only on the assemblages of polybiomes. This is a departure from the conventional approach, which focuses only on the ways in which poly-biome assemblages communicate with one another [159,160]. These techniques may provide a clinical evaluation because they can provide accuracy at the species level for taxonomy, analyze transmission pathways, and quantify the physiological activities that occur within one diverse microbiota composition [161]. This is reasonable considering that, when combined, meta-omic approaches may provide phylogenetic accuracy down to the genus level. Evidence for the idea that host signals in type 2 diabetes alter the biodiversity and GI tract microbiota metabolic pathways of the colonic microbiota was found in digital high-throughput sequencing of bacterial genomes and metabolic engineering in the ileal secretions of mice with UC Davis type 2 diabetes mellitus (UCD T2DM) [162]. Throughout this investigation, modifications were made for a range of characteristics, including diet, maturity level, and socioeconomic situations. One of the most interesting elements of this strategy is that it was effective in establishing statistically significant linkages between any of the bowel microbiota and therapeutic intervention methods, utilizing simulations of intestine-related processes and poly-biomes in the gut to study how they socialize [163]. Both gastrointestinal tract poly-biome metabolic pathways and microbiota are capable of bioactivity on intestinal epithelial cells. The intestinal mucosa is the first layer of tissue to be examined in the attempt to find biochemical processes and bacteria linked with the gastrointestinal milieu. In one example, such complexes are considered fiber-derived compounds [164]. A good example would be lipids with a relatively short chain of carbon atoms, often known as short-chain fatty acids in the scientific world [165]. Short-chain fatty acids are composed of hydrocarbons with heterocyclic terminals of 1–6 carboxyl groups, the most common of which are acetic acid, propionic acid, and butyric acid, all of which are produced in the gut by the autotrophic state of nutritious natural fibers [166]. Several physiological fluids have been studied in order to determine whether or not these gastrointestinal tract poly-biome metabolic pathways are present [167, 168]. Even while the relevance of researching beneficial bacteria and the metabolic products they produce in relation to nutrition has grown, it is still unclear what function they play in the endothelium that surrounds and supports the human gut [169-174]. The secretion of intercellular neurotransmitters is a kind of cross-talk in which the target network is in close proximity to the communicating neuron. The effects of short-chain fatty acids on this expression have been investigated, with the goal of determining whether or not they stimulate it [175]. A negative reaction, the development of fibrous material, the repair of cellular components, and the platelet aggregation of bleeding are all examples of cellular reactions to nutrients [176]. Butyric acid, which is also known by its racemic mixture, boosted the synthesis of aldehyde dehydrogenases 1A1 and 1A3, depending on whether it was given to mice or humans [178]. Butyric acid is also well known by its racemic mixture. For beta-carotene or provitamin A (retinol) to be converted into retinoids, epithelial tissue requires the development of aldehyde dehydrogenase 1A1-3. The discovery of a novel method for synthesizing vitamin A from butyrate is critical to understanding how the gut mucosa and microorganisms interact in the instinctive biosphere [179]. Finally, it has been proposed that neurotransmission-secretory granule cells function as immunosensors in gut epithelial tissue. As a result, they include data relevant to diverse pharmacological sensory stimuli directed further toward the ventral tegmental region in cooperation with peripheral cell lines originating from patient tumors [180,181]. Researchers conducted an investigation to see whether or not preclinical analytic methodologies might be used to assist in gaining a better knowledge of the operation of additional enzymatic processes for the gut microbial population [182]. According to the results of this research, endocrine cells have distinct chemosensory receptors, are electrically excitable, and regulate serotonin-sensitive primary afferent nerve fibers through synaptic connections. These intracellular signaling pathway cells are the most prevalent kind of intestinal epithelial cells, and they may gather information about gut health, metabolism, and other homeostatic processes before transmitting it directly to the hippocampus [183]. Neurotransmission secretory granule cells were both selective and persistent in their responses to propyl glycoside, the ethyl ester of isovaleric acid, dopamine, and norepinephrine. Intracellular calcium ions, on the other hand, produced only mild but predictable responses from the short-chain fatty acids. With these novel discoveries, gastro-intestinal patient-derived RNA presents a unique biological method for examining the sensory information provided by the gastro-intestinal commensal RNA biome. It is easier to study how biologically active substances affect the intestinal mucosa than it is to find bacteria [184]. In order to simulate a real-world scenario, it is important to introduce bacteria into the spheroid lumen and, if at all feasible, complex combinations of microbial populations. However, a number of substantial technological challenges develop as a consequence of this. So far, three methods have been used to deliver bacteria into patients: pronuclear microinjection, ruptured xenografts patient-derived, and two-dimensional colonies created from colon tissue patient-derived samples. The physical and physiological similarities between genetically modified mouse spheroids are startling [185]. When induced pluripotent stem cells are disrupted, the apical side is exposed; at this moment, fragmented cells may interact with microorganisms [186]. This pertains to the very first possible outcome. Probiotics have been proven in several investigations to protect conjunctival lymphocytes and co-culture stratified squamous epithelium and lymphoid cells. The probiotic Lactobacillus has been extensively researched and is a crucial component in maintaining the mucosal barrier [187]. Nonetheless, little is known about the role of the stem cell niche in this innovative treatment. The results imply that necrosis factor alpha (TNF alpha) maintained probiotic Lactobacillus spheroids intact. As a consequence, despite the fact that more LGR5-expressing cells were found, this antibody has not been tested on epithelium derived mostly from LGR5, a stem cell biomarker in mouse thin and thick bowel defective mice. The researchers proposed that probiotic lactobacillus causes lymphoid stratified squamous epithelium to produce more

interleukin-22 through networking with receptor sites in the direction of aromatic aldehyde hydrocarbons [187]. When this takes place, the transmission regulator and promoter of expression 3, which is responsible for accelerating the process of intestinal stem cell regeneration, becomes phosphorylated. You can also show the apical part of neural stem cells by breaking them up into single cells and then putting them on an extracellular matrix or coated plate [188]. Depending on the circumstances, this may be done in a number of ways. Following the conclusion of this technique, the bacteria are directly introduced into the growing medium. As a result, the bacteria and the host tissue monolayer may work together [189]. In recent years, a completely novel approach for reversing the polarity of the patient-derived has been created. This approach includes everting the apex's surface such that it resembles the medium. The mechanism that drives this strategy is known as the "split-face" method [190]. this cutting-edge and practical model may investigate barrier integrity and nutrient intake, and it has the potential to open up new avenues of investigation into the interactions between dietary items, the colonic poly-biome, and the gut epithelium [191]. Despite the fact that the majority of the procedures presented here have been proven using aerobic bacteria, anaerobic microbes make up the great majority of microbes that may be identified in the gut. Researchers have studied the anaerobic microbiota utilizing human stem cell lines by introducing foreign live bacteria into the lumen of patient-derived cells. This approach was required because biospecimen lines proliferate and alter the quickest when there is ample oxygen [192]. There was no other way to solve the situation. These investigations were made feasible using a high-throughput microinjection approach. This approach ensured that injections of induced pluripotent stem cells into the intestinal lumen were both effective and secure. The study also showed that, after fecal transplant, either aerobic or anaerobic ecosystems could be transferred into the patient's intestinal lumen and cultured for 96 hours with a remarkable lack of variation in the relative composition of the bacterial communities. The proportionate composition of the microbial communities altered relatively little, which provided support for this. As proof for this, we might look to the fact that the relative mix of the different microbial communities did not vary much from one instance to the next. Due to the fact that the number of brain stem cells and their size might vary from one individual to the next, it is critical to have a constant microbial payload. This is because the dimensional properties of the organisms being carried impact this variation. This technological advancement might significantly enhance new techniques for investigating complicated microbial populations, leading to significant medical discoveries. A connection must be established between these data points in order to ascertain if they correctly describe the events that occur inside the gut microbiota. The fact that the data come from some in vivo testing makes this significant [193-196].

Methods for Assessing the Reactivity of Intestinal Organoids to the Microbiome and Metabolic Products Aspects of Interactions, from Massive Cells to Specific Cells

It showed that the gastrointestinal patient-derived interaction, including the use of tumor microenvironment research techniques, is influenced by the typical microbe that inhabits the digestive system. Utilizing a variety of multi-omics technologies is crucial to completely comprehend how efficiently these activities and the responses they trigger are regulated in the intestinal mucosa. Tissue samples, disintegrating tissues, or cultures have been used in the great majority of high-throughput sequencing investigations to assess the increased amounts of epigenetic changes, genomics, or enzymatic activities [197, 198]. By creating microscopic cells across the exo- and intra-metabolomes of gastrointestinal patient-derived cells, it is feasible to shed light on crucial metabolic processes that affect tumoroids and gastrointestinal patient-derived cells. This is plausible given that bioactive substances are both the products of genetic material and the ecological changes that take place. The majority of the geospatial data, architecture, and heterogeneous nature, which are essential for understanding the fundamentals of these kinds of complex and sophisticated network interactions, are excluded from total high-throughput sequencing approaches like protein engineering and metaproteomics. Deep picture management and analysis is a cutting-edge technique that is useful in the digital world of research into tumor cross-sectional dependency [199-201]. This action was taken in an effort to get around the limitations mentioned before. Therefore, intestinal 3D bioprinting epithelium may detect the intracellular transfer of certain intestinal microbiota macromolecules using high-throughput angiography. Additionally, it may reliably identify the biochemical actions of such substances as well as the vascular endothelium's metabolic or metabolomic hysterical reactions to the tissue [202-204]. Molecular species that are known or unknown may be found, and their global distribution can be measured. by identifying the locations and ranges of single-molecule entities inside a certain region. There are many different ways to define cells when using the "huge amounts" of highly high sequence alignment approaches. This could make analyzing such data sets challenging. It seems that distinct metabolic pathways constantly emerge at the single-cell level, and responses to biochemical signal transduction pathways may vary. The characterization of individual cells is becoming a growing issue in the fields of genetics, metaproteomics, genetic fingerprinting, systems biology, and metabolic engineering [205-207]. A single-cell RNA sequence analysis dataset, revealed the cellular communities in gastrointestinal patient-derived cells cultured with a variety of signaling pathways, as well as the spatial organization of various cellular processes and physiological responsiveness to infectious diseases, particularly salmonella poisoning [209-211]. These cutting-edge concepts are difficult to adopt due to cost and technological challenges. In large-scale methods, there can be a growing need for longitudinal spectral resolution and precision. Despite this, they could later come up with original and creative methods to contribute. So, high-throughput and metatranscriptomics of three-dimensional gastrointestinal patients are now possible. This lets researcher's look at the spread of regulatory sequences and signaling pathways at the molecular and cellular levels [212-214].

Future Concepts and Opinions Examined

The quest for state-of-the-art knowledge on diet, healthy eating habits, and the microbiota in the gut is ongoing. Polybiome bioactive compounds located in the gastrointestinal tract include a complex role for the colon's microbiota. To take this approach, we need to discover new enzymatic indicators and create novel therapy methods based only on macronutrient and micronutrient supplementation tailored to each individual patient. This has been verified by a plethora of research. Biotransformation networks emerge in the digestive system as a result of the adoption of many techniques [215, 216]. The composition of the intestinal microbiota, dietary factors, and the microbiota's homeostasis processes may all be important for preserving the integrity of the host cell membrane. Pathogenic bacteria in the

gut microbiota may be able to more readily employ metabolic pathways that encourage their proliferation when we consume foods that represent our contemporary way of life [217-219]. Because of this, potentially hazardous microbes have a better chance to spread disease. These metabolic networks are linked to the slow but steady progression of a potentially lethal disease that is toxic to mucosal surfaces. The fatality rate rises as a result of this illness. Many various types of bodily fluids, such as blood and tissue, as well as the beneficial bacteria that are prevalent in large bowel ecosystems, have been the primary focus of recent investigations [220-223]. The majority of studies have focused on the beneficial microorganisms that naturally occur in the colon. Even while recent algorithms have demonstrated that there are considerable connections between the human intestinal microbiota and colonic illnesses, very little can be mentioned regarding how the metabolic activities and gene mutations of the microbial community impact colon tissue growth. [224]. This is still the case. Current algorithms used to discover ways do not indicate a connection between the gut microbiota and colonic diseases in patients, yet this is the case. It's possible to observe epithelial cell activity in vitro using models of the gastrointestinal system produced from individual patients. It has been demonstrated in recent research that this is the case. It's possible that the information presented here might be useful in dealing with a wide range of diseases. Patient information was used to create these models. To sum up, having healthy tumoroids and cells in the gastrointestinal tract has several benefits. By contrasting the epithelium in healthy individuals with that of patients with a disease, researchers may learn more about the processes that progenitor cells participate in. Protein production, distribution, and function may now be studied in depth, in addition to the electrochemical signaling systems activated by biomaterials included in the components. Also, it sheds light on the body's protein synthesis, transport, and use processes. Long-standing issues concerning the impact of these metabolic pathways on health and illness will be answered by research into the poly-biome in the gastrointestinal tract, the relationship between the colon epithelial layer and the microbial population, and patient-derived microbiota data [225-228]. Queries will be answered with the use of meta-data related to the poly-biome of the digestive system and the metabolic pathways used by bacteria. Further, an experiment that mirrors the first stage in terms of preparation and execution might be useful. We predict that soon intestine tissue samples will be used in various contexts. The uses for these things are varied. Improved diagnosis and treatment of digestive illnesses may be achieved via research into the link between nutrient-rich foods, gut microbiota, and the organisms presently serving as hosts [229-232]. Patient-derived models are now widely available, allowing their usage by researchers from all across the world. They're utilized all across the world on the most important parts of the digestive system and are often referred to as bowel prototypes. Lifestyle treatments' effects on the gastrointestinal tract's pathogenic processes and tissue-specific and metabolic capacities will be studied in greater depth in the near future with the use of these models. There are occasions when biologists will assert that a tissue sample, colon tissue from patient-derived tumor model, or spheroids seem to be considerably more similar to a digestive tract [233-236]. The parts may have been used interchangeably, yet they each have their own unique characteristics. Modern methods and progenitor cells allow for the cultivation of spheroids in the microbiology lab. Probiotic researchers may find significant help from a novel technique that employs xenografts to construct miniature gut tissues in the lab. It would turn out well and cost less than what they had already paid [237-239]. When applied to a field outside of regenerative medicine, we believe that gut organotypic analysis offers a fresh perspective on the technique [240]. Therefore, this icon represents the digestive system as a whole, not just one part of it. Since all cells spontaneously release hormones and generate a spectrum of bioactive substances, this strategic approach is not only more powerful than the prior in silico analysis, but it is also very cost-effective. This is due to the fact that hormones are created by every single cell in the body [241, 242].

Discussion

The progression of illnesses such colon cancer metastases, which may affect intestinal lumen homeostasis, is controlled by the disease, dietary behavior patterns, dysbacteriosis of the microbial population, and gastrointestinal endophytic mediators [243-247]. Most models used to decode food, microbiota, and host interactions are animal-based. Animals are excellent for investigating these complicated interactions. This is due to several factors, including the fact that gut intermediates and bacteria play important roles in many biological processes. Furthermore, this is true if we agree that chemical agents and gut microorganisms play important regulatory functions. Gut microbiota's tiny organisms and bioactive components play a key function in physiological decision-making [248-250]. This is despite being formed by gut microbes. Because of gastrointestinal allografts, in vitro platforms may now simulate healthy and pathological diet-microbiome-host scenarios. Before in vitro platforms, this was impossible. Advances in tissue engineering make this possible [251]. It is now possible for colonic organoids to simulate the complicated direct and indirect relationships between ingredients, gut bacteria, and the current host. Analyzing how an intestine, stomach, or liver transplant reacts to biologically active compounds produced by gut microorganisms may provide novel insights into how these compounds either prevent or induce illness [252, 253]. This study will assist us in gaining a better understanding of the intricate relationships that exist between nutrition, the microbiota in the gut, and the host, and will provide new horizons for the exploration and management of diseases of the gastrointestinal tract. But many questions remain about how gut bacteria or chemicals may benefit human health Dietary habits have been shown to be connected with population health; nevertheless, many issues remain unanswered about the processes through which bacteria or gastrointestinal microbiota byproducts might very well elicit therapeutic advantages. Colonic xenografts may lend credibility to the discoveries of noncommunicable diseases and nutritional surveys and questionnaires, as well as shed light on the mechanisms involved. [254,255]. The make-up of an individual's gastrointestinal microbiota has a direct bearing on the kinds of byproducts that are created by the microbes that reside there, as well as the amount of those byproducts and the physicochemical characteristics they exhibit. is it really possible for colonic patient - derived to expose the molecular reactions to these variations in the dynamic environment? When it comes to rewiring dysfunctional pathways linked to gut disorders like colon cancer, may targeting the intestinal- epigenome using gastrointestinal microbiota biomolecules be a consistently effective strategic approach? After that, is it possible to identify gastrointestinal microbiota byproducts and thereafter link them to the healthy and natural phytonutrients and microorganisms that are fully accountable for microbiological oxidative metabolism? [255]. If true, this might reprogramme aberrant pathways connected to these diseases.

Alzheimer's, Parkinson's, and multiple sclerosis are examples. How much might the advantageous effects of some metabolites, such as the activation of multiple signaling pathways in the host, consisting primarily of acetate, propionate, butyrate, or phenolic acids, flavonoids, coumarins, and curcuminoids, which are produced through gut microbial fermentation, offset the destructive properties of some of the other metabolites, such as trimethylamine, trimethylamine N-oxide, secondary bile salts such as deoxycholic acid (DOC) and lithocholic acid? Are colonic organoids, on the other hand, equally able to display these direct connections? There is constant development of better colonic patient - derived. However, is it possible to co-culture them with other biological materials that are available in preclinical studies, such as neurons, tissues, and abdominal muscles, and then investigate the consequences of doing so?

Declarations

Conflicts of Interest

This author confirms that they have no conflicts of interest that might be seen as influencing their work in any way.

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References

1. Goñi I, Hernández Galiot A (2019) Intake of Nutrient and Non-Nutrient Dietary Antioxidants. Contribution of Macromolecular Antioxidant Polyphenols in an Elderly Mediterranean Population. Nutrients 11: 2165.
2. González S, Fernández M, Cuervo A, Lasheras C (2014) Dietary intake of polyphenols and major food sources in an institutionalised elderly population. J Hum Nutr Diet 27: 176-83.
3. Scalbert A, Williamson G (2000) Dietary intake and bioavailability of polyphenols. J Nutr 130: 2073S-2085S.
4. Gupta C, Prakash D (2014) Phytonutrients as therapeutic agents. J Complement Integr Med 11: 151-169.
5. Monjotin N, Amiot MJ, Fleurentin J, Morel JM, Raynal S (2022) Clinical Evidence of the Benefits of Phytonutrients in Human Healthcare. Nutrients 14: 1712.
6. Wang Z, Guo M, Lim SS (2022) Editorial: Recent advances in recognition of bioactive phytonutrients for specific targets in plant foods. Front Nutr 9: 1018946.
7. Kopytina V, Pascual Antón L, Toggweiler N, Arriero País EM, Strahl L et al. (2022) Steviol glycosides as an alternative osmotic agent for peritoneal dialysis fluid. Front Pharmacol 13: 868374.
8. Benković G, Bojić M, Maleš Ž, Tomić S (2019) Screening of flavonoid aglycons' metabolism mediated by the human liver cytochromes P450. Acta Pharm 69: 541-562.
9. Latos Brozio M, Masek A, Piotrowska M (2022) Polymeric Forms of Plant Flavonoids Obtained by Enzymatic Reactions. Molecules 27: 3702.
10. Stéphanie Déprez, Christophe Brezillon, Sylvie Rabot, Catherine Philippe, Isabelle Mila et al. (2000) Polymeric Proanthocyanidins Are Catabolized by Human Colonic Microflora into Low-Molecular-Weight Phenolic Acids, The Journal of Nutrition 130: 2733-2738.
11. Chen Zhongjian, Zheng Shirui, Li Liping, Jiang Huidi (2014) Metabolism of Flavonoids in Human: A Comprehensive Review, Current Drug Metabolism 15: 48-61.
12. Bazzocco S, Mattila I, Guyot S, Renard CM, Aura AM (2008) Factors affecting the conversion of apple polyphenols to phenolic acids and fruit matrix to short-chain fatty acids by human faecal microbiota in vitro. Eur J Nutr 47: 442-452.
13. Aura AM, Mattila I, Hyötyläinen T, Gopalacharyulu P, Cheynier V (2013) Characterization of microbial metabolism of Syrah grape products in an in vitro colon model using targeted and non-targeted analytical approaches. Eur J Nutr 52: 833-846.
14. Mezhibovsky E, Knowles KA, He Q, Sui K, Tveter KM et al. (2021) Grape Polyphenols Attenuate Diet-Induced Obesity and Hepatic Steatosis in Mice in Association With Reduced Butyrate and Increased Markers of Intestinal Carbohydrate Oxidation. Front Nutr 14: 675267.
15. Wan MLY, Ling KH, El-Nezami H, Wang MF (2019) Influence of functional food components on gut health. Crit Rev Food Sci Nutr 59: 1927-1936.
16. Duda-Chodak A, Tarko T, Satora P, Sroka P (2015) Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. Eur J Nutr 54: 325-341.
17. Barakat H, Aljutaily T, Almujaydil MS, Algheshairy RM, Alhomaid RM et al. (2022) Amygdalin: A Review on Its Characteristics, Antioxidant Potential, Gastrointestinal Microbiota Intervention, Anticancer Therapeutic and Mechanisms, Toxicity, and Encapsulation. Biomolecules 12: 1514.
18. Zhang X, Gérard P (2022) Diet-gut microbiota interactions on cardiovascular disease. Comput Struct Biotechnol J 20: 1528-1540.
19. Gasaly N, de Vos P, Hermoso MA (2021) Impact of Bacterial Metabolites on Gut Barrier Function and Host Immunity: A Focus on Bacterial Metabolism and Its Relevance for Intestinal Inflammation. Front Immunol 26: 658354.
20. Vourakis M, Mayer G, Rousseau G (2021) The Role of Gut Microbiota on Cholesterol Metabolism in Atherosclerosis. Int J Mol Sci 22: 8074.
21. Man AWC, Zhou Y, Xia N, Li H (2020) Involvement of Gut Microbiota, Microbial Metabolites and Interaction with Polyphenol in Host Immunometabolism. Nutrients 12: 3054.
22. Guertin KA, Li XS, Graubard BI, Albanes D, Weinstein SJ et al. (2017) Serum Trimethylamine N-oxide, Carnitine, Choline, and Betaine in Relation to Colorectal Cancer Risk in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study. Cancer Epidemiol Biomarkers Prev 26: 945-952.
23. Fu BC, Hullar MAJ, Randolph TW, Franke AA, Monroe KR et al. (2020) Associations of plasma trimethylamine N-oxide, choline, carnitine, and betaine with inflammatory and cardiometabolic risk biomarkers and the fecal microbiome in the Multiethnic Cohort Adiposity Phenotype Study. Am J Clin Nutr 111: 1226-1234.
24. Cho D, Milbury K, Liao Y, Pettaway CA, Gregg JR et al. (2021) Study protocol: One plus one can be greater than two-Ecological momentary assessment for Black prostate cancer survivors and partners. PLoS One 16: e0255614.
25. Larsson SC, Bergkvist L, Wolk A (2006) Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 15: 1998-2001.
26. Di Maso M, Dal Maso L, Augustin LSA, Puppo A, Falcini

F et al. (2020) Adherence to the Mediterranean Diet and Mortality after Breast Cancer. Nutrients 12: 3649.
27. Schulpen M, van den Brandt PA (2021) Adherence to the Mediterranean Diet and Overall Cancer Incidence: The Netherlands Cohort Study. J Acad Nutr Diet 121: 242-252.
28. Allicock M, Kendzor D, Sedory A, Gabriel KP, Swartz MD et al. (2021) Thomas P, Yudkin JS, Rivers A. A Pilot and Feasibility Mobile Health Intervention to Support Healthy Behaviors in African American Breast Cancer Survivors. J Racial Ethn Health Disparities 8: 157-165.
29. Zucchetto A, Gini A, Shivappa N, Hébert JR, Stocco C et al. (2016) Dal Maso L, Birri S, Serraino D, Polesel J. Dietary inflammatory index and prostate cancer survival. Int J Cancer 139: 2398-2404.
30. Di Maso M, Augustin LSA, Toffolutti F, Stocco C, Dal Maso L et al. (2021) Jenkins DJA, Fleshner NE, Serraino D, Polesel J. Adherence to Mediterranean Diet, Physical Activity and Survival after Prostate Cancer Diagnosis. Nutrients 13: 243.
31. Cena H, Calder PC (2020) Defining a Healthy Diet: Evidence for The Role of Contemporary Dietary Patterns in Health and Disease. Nutrients 12: 334.
32. Yang J, Yu J (2018) The association of diet, gut microbiota and colorectal cancer: what we eat may imply what we get. Protein Cell 9: 474-487.
33. Gao S, Khan MI, Kalsoom F, Liu Z, Chen Y et al. (2022) Role of gene regulation and inter species interaction as a key factor in gut microbiota adaptation. Arch Microbiol 204: 342.
34. Hills RD Jr, Pontefract BA, Mishcon HR, Black CA, Sutton SC et al. (2019) Gut Microbiome: Profound Implications for Diet and Disease. Nutrients 11: 1613.
35. Li Q, Lauber CL, Czarnecki-Maulden G, Pan Y, Hannah SS (2017) Effects of the Dietary Protein and Carbohydrate Ratio on Gut Microbiomes in Dogs of Different Body Conditions. mBio 8: e01703-1716.
36. Li Q, Pan Y (2020) Differential Responses to Dietary Protein and Carbohydrate Ratio on Gut Microbiome in Obese vs. Lean Cats. Front Microbiol 11: 591462.
37. Hooda S, Vester Boler BM, Kerr KR, Dowd SE, Swanson KS (2013) The gut microbiome of kittens is affected by dietary protein:carbohydrate ratio and associated with blood metabolite and hormone concentrations. Br J Nutr 109: 1637-1646.
38. Deng P, Swanson KS (2015) Gut microbiota of humans, dogs and cats: current knowledge and future opportunities and challenges. Br J Nutr 113: S6-17.
39. Kusari S, Hertweck C, Spiteller M (2012) Chemical ecology of endophytic fungi: origins of secondary metabolites. Chem Biol 19: 792-798.
40. El Hawary SS, Moawad AS, Bahr HS, Abdelmohsen UR, Mohammed R (2020) Natural product diversity from the endophytic fungi of the genus Aspergillus. RSC Adv 10: 22058-22079.
41. Doyle VC (2007) Nutrition and colorectal cancer risk: a literature review. Gastroenterol Nurs 30: 178-182.
42. Mathew A, Peters U, Chatterjee N, Kulldorff M, Sinha R (2004) Fat, fiber, fruits, vegetables, and risk of colorectal adenomas. Int J Cancer 108: 287-292.
43. Collins RA, Baker B, Coyle DH, Rollo ME, Burrows TL (2020) Dietary Assessment Methods in Military and Veteran Populations: A Scoping Review. Nutrients 12: 769.
44. Ferguson EF Jr, McKibben BT (1990) Preventing colorectal cancer. South Med J 83: 1295-1299.
45. Guibourdenche M, Haug J, Chevalier N, Spatz M, Barbezier N et al. (2021) Food Contaminants Effects on an In Vitro Model of Human Intestinal Epithelium. Toxics 9: 135.
46. Ponce de León-Rodríguez MDC, Guyot JP, Laurent-Babot C (2019) Intestinal in vitro cell culture models and their potential to study the effect of food components on intestinal inflammation. Crit Rev Food Sci Nutr 59: 3648-3666.
47. Barsby JP, Cowley JM, Leemaqz SY, Grieger JA, McKeating DR et al. (2021) Perkins AV, Bastian SEP, Burton RA, Bianco-Miotto T. Nutritional properties of selected superfood extracts and their potential health benefits. PeerJ 9: e12525.
48. Alassane Kpembi I, Puel O, Oswald IP (2015) Toxicological interactions between the mycotoxins deoxynivalenol, nivalenol and their acetylated derivatives in intestinal epithelial cells. Arch Toxicol 89: 1337-1346.
49. Pinton P, Oswald IP (2014) Effect of deoxynivalenol and other Type B trichothecenes on the intestine: a review. Toxins (Basel) 6: 1615-1643.
50. Pearce SC, Coia HG, Karl JP, Pantoja Feliciano IG, Zachos NC et al. (2018) Intestinal in vitro and ex vivo Models to Study Host-Microbiome Interactions and Acute Stressors. Front Physiol 9: 1584.
51. Moossavi S, Arrieta MC, Sanati Nezhad A, Bishehsari F (2022) Gut-on-chip for ecological and causal human gut microbiome research. Trends Microbiol 30: 710-721.
52. Jeon MS, Choi YY, Mo SJ, Ha JH, Lee YS et al. (2022) Contributions of the microbiome to intestinal inflammation in a gut-on-a-chip. Nano Converg 9: 8.
53. Shin W, Hackley LA, Kim HJ (2020) "Good Fences Make Good Neighbors": How does the Human Gut Microchip Unravel Mechanism of Intestinal Inflammation? Gut Microbes11: 581-586.
54. Balcerczyk A, Damblon C, Elena-Herrmann B, Panthu B, Rautureau GJP (2020) Metabolomic Approaches to Study Chemical Exposure-Related Metabolism Alterations in Mammalian Cell Cultures. Int J Mol Sci 21: 6843.
55. Brasili E, Filho VC (2017) Metabolomics of cancer cell cultures to assess the effects of dietary phytochemicals. Crit Rev Food Sci Nutr 57: 1328-1339.
56. Warth B, Raffeiner P, Granados A, Huan T, Fang M et al. (2018) Forsberg EM, Benton HP, Goetz L, Johnson CH, Siuzdak G. Metabolomics Reveals that Dietary Xenoestrogens Alter Cellular Metabolism Induced by Palbociclib/Letrozole Combination Cancer Therapy. Cell Chem Biol 25: 291-300e3.
57. Mena P, Bresciani L, Brindani N, Ludwig IA, Pereira Caro G et al. (2019) Phenyl-γ-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: synthesis, analysis, bioavailability, and bioactivity. Nat Prod Rep 36: 714-752.
58. Choy YY, Fraga M, Mackenzie GG, Waterhouse AL, Cremonini E et al. (2016) The PI3K/Akt pathway is involved in procyanidin-mediated suppression of human colorectal cancer cell growth. Mol Carcinog 55: 2196-2209.
59. Yadav M, Verma MK, Chauhan NS (2018) A review of metabolic potential of human gut microbiome in human nutrition. Arch Microbiol 200: 203-217.
60. Chittim CL, Irwin SM, Balskus EP (2018) Deciphering Human Gut Microbiota-Nutrient Interactions: A Role for Biochemistry. Biochemistry 57: 2567-2577.
61. Vernocchi P, Del Chierico F, Putignani L (2020) Gut Microbiota Metabolism and Interaction with Food Components. Int J Mol Sci 21: 3688.

62. Lyte JM, Keane J, Eckenberger J, Anthony N, Shrestha S et al. (2021) Japanese quail (Coturnix japonica) as a novel model to study the relationship between the avian microbiome and microbial endocrinology-based host-microbe interactions. Microbiome 9: 38.
63. Ribeiro JA, Dos Santos Pereira E, de Oliveira Raphaelli C, Radünz M, Camargo TM et al. (2022) Application of prebiotics in apple products and potential health benefits. J Food Sci Technol 59: 1249-1262.
64. Rezende ESV, Lima GC, Naves MMV (2021) Dietary fibers as beneficial microbiota modulators: A proposed classification by prebiotic categories. Nutrition 89: 111217.
65. Caini S, Chioccioli S, Pastore E, Fontana M, Tortora K et al. (2022) Caderni G, Masala G. Fish Consumption and Colorectal Cancer Risk: Meta-Analysis of Prospective Epidemiological Studies and Review of Evidence from Animal Studies. Cancers (Basel) 14: 640.
66. Ekine Afolabi BA, Njan AA, Rotimi SO, R I A, Elbehi AM et al. (2020) The Impact of Diet on the Involvement of Non-Coding RNAs, Extracellular Vesicles, and Gut Microbiome-Virome in Colorectal Cancer Initiation and Progression. Front Oncol 10: 583372.
67. Bull Larsen S, Mohajeri MH (2019) The Potential Influence of the Bacterial Microbiome on the Development and Progression of ADHD. Nutrients 11: 2805.
68. Williamson G, Kay CD, Crozier A (2018) The Bioavailability, Transport, and Bioactivity of Dietary Flavonoids: A Review from a Historical Perspective. Compr Rev Food Sci Food Saf 17: 1054-1112.
69. Chen Y, Hamidu S, Yang X, Yan Y, Wang Q et al. (2022) Dietary Supplements and Natural Products: An Update on Their Clinical Effectiveness and Molecular Mechanisms of Action During Accelerated Biological Aging. Front Genet 13: 880421.
70. Gasperotti M, Passamonti S, Tramer F, Masuero D, Guella G et al. (2015) Fate of microbial metabolites of dietary polyphenols in rats: is the brain their target destination? ACS Chem Neurosci 16: 1341-1352.
71. Raimundo AF, Ferreira S, Tomás-Barberán FA, Santos CN, Menezes R (2021) Urolithins: Diet-Derived Bioavailable Metabolites to Tackle Diabetes. Nutrients 13: 4285.
72. He Y, Zhang Y, Li F, Shi Y (2022) White Matter Injury in Preterm Infants: Pathogenesis and Potential Therapy From the Aspect of the Gut-Brain Axis. Front Neurosci 16: 849372.
73. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA et al. (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341: 569-573.
74. Lagkouvardos I, Pukall R, Abt B, Foesel BU, Meier Kolthoff JP et al. (2016) The Mouse Intestinal Bacterial Collection (miBC) provides host-specific insight into cultured diversity and functional potential of the gut microbiota. Nat Microbiol 1: 16131.
75. Hugenholtz F, de Vos WM (2018) Mouse models for human intestinal microbiota research: a critical evaluation. Cell Mol Life Sci 75: 149-160.
76. Ercolini D, Fogliano V (2018) Food Design to Feed the Human Gut Microbiota. J Agric Food Chem 66: 3754-3758.
77. Walter J, Armet AM, Finlay BB, Shanahan F (2020) Establishing or Exaggerating Causality for the Gut Microbiome: Lessons from Human Microbiota-Associated Rodents. Cell 180: 221-232.
78. Sears CL (2022) Microbes and cancer: disease drivers, passengers, biomarkers, or therapeutics? Cancer Metastasis Rev 41: 247-248.
79. Deehan EC, Zhang Z, Riva A, Armet AM, Perez-Muñoz ME et al. (2022) Nguyen NK, Krysa JA, Seethaler B, Zhao YY, Cole J, Li F, Hausmann B, Spittler A, Nazare JA, Delzenne NM, Curtis JM, Wismer WV, Proctor SD, Bakal JA, Bischoff SC, Knights D, Field CJ, Berry D, Prado CM, Walter J. Elucidating the role of the gut microbiota in the physiological effects of dietary fiber. Microbiome 10: 77.
80. Belizário JE, Faintuch J (2018) Microbiome and Gut Dysbiosis. Exp Suppl 109: 459-476.
81. Twardowska A, Makaro A, Binienda A, Fichna J, Salaga M (2022) Preventing Bacterial Translocation in Patients with Leaky Gut Syndrome: Nutrition and Pharmacological Treatment Options. Int J Mol Sci 23: 3204.
82. Mousa WK, Chehadeh F, Husband S (2022) Recent Advances in Understanding the Structure and Function of the Human Microbiome. Front Microbiol 13:825338.
83. Date S, Sato T (2015) Mini-gut organoids: reconstitution of the stem cell niche. Annu Rev Cell Dev Biol 31: 269-289.
84. Bae J, Choi YS, Cho G, Jang SJ (2022) The Patient-Derived Cancer Organoids: Promises and Challenges as Platforms for Cancer Discovery. Cancers (Basel) 14: 2144.
85. Gu W, Colarusso JL, Dame MK, Spence JR, Zhou Q (2022) Rapid establishment of human colonic organoid knockout lines. STAR Protoc 3: 101308.
86. Sun CP, Lan HR, Fang XL, Yang XY, Jin KT (2022) Organoid Models for Precision Cancer Immunotherapy. Front Immunol 13: 770465.
87. Berg HF, Hjelmeland ME, Lien H, Espedal H, Fonnes T et al. (2021) Patient-derived organoids reflect the genetic profile of endometrial tumors and predict patient prognosis. Commun Med (Lond) 1: 20.
88. Wang X (2019) Stem cells in tissues, organoids, and cancers. Cell Mol Life Sci 76: 4043-4070.
89. Suarez Martinez E, Suazo Sanchez I, Celis Romero M, Carnero A (2022) 3D and organoid culture in research: physiology, hereditary genetic diseases and cancer. Cell Biosci 12: 39.
90. Sugimoto S, Sato T (2017) Establishment of 3D Intestinal Organoid Cultures from Intestinal Stem Cells. Methods Mol Biol 1612: 97-105.
91. Qi Z, Chen YG (2015) Regulation of intestinal stem cell fate specification. Sci China Life Sci 58: 570-578.
92. Taelman J, Diaz M, Guiu J (2022) Human Intestinal Organoids: Promise and Challenge. Front Cell Dev Biol 10: 854740.
93. Altay G, Larrañaga E, Tosi S, Barriga FM, Batlle E et al. (2019) Self-organized intestinal epithelial monolayers in crypt and villus-like domains show effective barrier function. Sci Rep 9: 10140.
94. Zietek T, Rath E, Haller D, Daniel H (2015) Intestinal organoids for assessing nutrient transport, sensing and incretin secretion. Sci Rep 5: 16831.
95. Rahman S, Ghiboub M, Donkers JM, van de Steeg E, van Tol EAF et al. (2021)The Progress of Intestinal Epithelial Models from Cell Lines to Gut-On-Chip. Int J Mol Sci 22: 13472.
96. Yin J, Tse CM, Avula LR, Singh V, Foulke Abel J et al. (2018) Molecular Basis and Differentiation-Associated Alterations of Anion Secretion in Human Duodenal Enteroid Monolayers. Cell Mol Gastroenterol Hepatol 5: 591-609.
97. Venkatasubramanian J, Ao M, Rao MC (2010) Ion transport in the small intestine. Curr Opin Gastroenterol 26: 123-128.

98. Ko CW, Qu J, Black DD, Tso P (2020) Regulation of intestinal lipid metabolism: current concepts and relevance to disease. Nat Rev Gastroenterol Hepatol 17: 169-183.
99. Yin S, Ray G, Kerschner JL, Hao S, Perez A et al. (2020) Functional genomics analysis of human colon organoids identifies key transcription factors. Physiol Genomics 52: 234-244.
100. Kitts DD, Wijewickreme AN (1994) Effect of dietary caffeic and chlorogenic acids on in vivo xenobiotic enzyme systems. Plant Foods Hum Nutr 45: 287-298.
101. Salbe AD, Bjeldanes LF (1985) The effects of dietary brussels sprouts and Schizandra chinensis on the xenobiotic-metabolizing enzymes of the rat small intestine. Food Chem Toxicol 23: 57-65.
102. Merker SR, Weitz J, Stange DE (2016) Gastrointestinal organoids: How they gut it out. Dev Biol 420: 239-250.
103. Kardia E, Frese M, Smertina E, Strive T, Zeng XL et al. (2021) Estes M, Hall RN. Culture and differentiation of rabbit intestinal organoids and organoid-derived cell monolayers. Sci Rep 11: 5401.
104. Kishida K, Pearce SC, Yu S, Gao N, Ferraris RP (2017) Nutrient sensing by absorptive and secretory progenies of small intestinal stem cells. Am J Physiol Gastrointest Liver Physiol 312: G592-G605.
105. Singh A, Poling HM, Spence JR, Wells JM, Helmrath MA (2020) Gastrointestinal organoids: a next-generation tool for modeling human development. Am J Physiol Gastrointest Liver Physiol 319: G375-G381.
106. Chen S, Xia Y, Zhu G, Yan J, Tan C et al. (2018) Glutamine supplementation improves intestinal cell proliferation and stem cell differentiation in weanling mice. Food Nutr Res 62:1-9.
107. Daniele B, D'Agostino L (1994) Proliferation and differentiation of the small intestinal epithelium: from Petri dish to bedside. Ital J Gastroenterol 26: 459-4570.
108. Abdallah FB, Fetoui H, Fakhfakh F, Keskes L (2012) Caffeic acid and quercetin protect erythrocytes against the oxidative stress and the genotoxic effects of lambda-cyhalothrin in vitro. Hum Exp Toxicol 31: 92-100.
109. Alam M, Ahmed S, Elasbali AM, Adnan M, Alam S et al. (2022) Hassan MI, Pasupuleti VR. Therapeutic Implications of Caffeic Acid in Cancer and Neurological Diseases. Front Oncol 12:860508.
110. Alam M, Ashraf GM, Sheikh K, Khan A, Ali Set al. (2022) Potential Therapeutic Implications of Caffeic Acid in Cancer Signaling: Past, Present, and Future. Front Pharmacol 13: 845871.
111. Cai M, Liu J, Song X, Qi H, Li Y et al. (2022) Wu Z, Xu H, Qiao M. De novo biosynthesis of p-coumaric acid and caffeic acid from carboxymethyl-cellulose by microbial co-culture strategy. Microb Cell Fact 21: 81.
112. Kawaguchi H, Katsuyama Y, Danyao D, Kahar P, Nakamura Tsuruta S et al. (2017) Caffeic acid production by simultaneous saccharification and fermentation of kraft pulp using recombinant Escherichia coli. Appl Microbiol Biotechnol 101: 5279-5290.
113. Amevor FK, Cui Z, Du X, Ning Z, Deng Xet al. (2022) Supplementation of Dietary Quercetin and Vitamin E Promotes the Intestinal Structure and Immune Barrier Integrity in Aged Breeder Hens. Front Immunol 13: 860889.
114. Feng ZM, Li TJ, Wu L, Xiao DF, Blachier F et al. (2015) Monosodium L-Glutamate and Dietary Fat Differently Modify the Composition of the Intestinal Microbiota in Growing Pigs. Obes Facts 8: 87-100.
115. Feng Z, Zhou X, Wu F, Yao K, Kong X et al. (2014) Both dietary supplementation with monosodium L-glutamate and fat modify circulating and tissue amino acid pools in growing pigs, but with little interactive effect. PLoS One 9: e84533.
116. Rohr MW, Narasimhulu CA, Rudeski Rohr TA, Parthasarathy S (2020) Negative Effects of a High-Fat Diet on Intestinal Permeability: A Review. Adv Nutr 11: 77-91.
117. Park JH, Lee JM, Lee EJ, Hwang WB, Kim DJ (2018) Indole-3-Carbinol Promotes Goblet-Cell Differentiation Regulating Wnt and Notch Signaling Pathways AhR-Dependently. Mol Cells 41: 290-300.
118. Gui X, Meng Z, McConnell YJ, Liu S, Falck VG et al. (2017) Differing expression profiles of Notch/enterocyte and Wnt/secretory lineage signallings are associated with morphological diversity of appendiceal tumours. J Clin Pathol 70: 40-50.
119. Schonhoff SE, Giel Moloney M, Leiter AB (2004) Minireview: Development and differentiation of gut endocrine cells. Endocrinology 145: 2639-2644.
120. Tao E, Zhu Z, Hu C, Long G, Chen B et al. (2022) Potential Roles of Enterochromaffin Cells in Early Life Stress-Induced Irritable Bowel Syndrome. Front Cell Neurosci 16: 837166.
121. Pham T, Teoh KT, Savary BJ, Chen MH, McClung A et al. (2017) In Vitro Fermentation Patterns of Rice Bran Components by Human Gut Microbiota. Nutrients 9: 1237.
122. Gu I, Lam WS, Marasini D, Brownmiller C, Savary BJ et al. (2021) In Vitro Fecal Fermentation Patterns of Arabinoxylan from Rice Bran on Fecal Microbiota from Normal-Weight and Overweight/Obese Subjects. Nutrients 13: 2052.
123. Nguyen NK, Deehan EC, Zhang Z, Jin M, Baskota N et al. (2020) Gut microbiota modulation with long-chain corn bran arabinoxylan in adults with overweight and obesity is linked to an individualized temporal increase in fecal propionate. Microbiome 8: 118.
124. Kumar J, Rani K, Datt C (2020) Molecular link between dietary fibre, gut microbiota and health. Mol Biol Rep 47: 6229-6237.
125. Gerhauser C (2008) Cancer chemopreventive potential of apples, apple juice, and apple components. Planta Med 74: 1608-1624.
126. Vallée Marcotte B, Verheyde M, Pomerleau S, Doyen A, Couillard C (2022) Health Benefits of Apple Juice Consumption: A Review of Interventional Trials on Humans. Nutrients 14: 821.
127. Tong Z, He W, Fan X, Guo A (2022) Biological Function of Plant Tannin and Its Application in Animal Health. Front Vet Sci 8: 803657.
128. Choy YY, Quifer Rada P, Holstege DM, Frese SA, Calvert CC et al. (2014) Phenolic metabolites and substantial microbiome changes in pig feces by ingesting grape seed proanthocyanidins. Food Funct 5: 2298-2308.
129. Choy YY, Jaggers GK, Oteiza PI, Waterhouse AL (2013) Bioavailability of intact proanthocyanidins in the rat colon after ingestion of grape seed extract. J Agric Food Chem 61: 121-127.
130. Goodrich KM, Smithson AT, Ickes AK, Neilson AP (2015) Pan-colonic pharmacokinetics of catechins and procyanidins in male Sprague-Dawley rats. J Nutr Biochem 26: 1007-1014.
131. Monagas M, Urpi Sarda M, Sánchez Patán F, Llorach R, Garrido I et al. (2010) Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and

the bioactivity of their metabolites. Food Funct 1: 233-253.
132. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J (2020) Flavonoids as Anticancer Agents. Nutrients 12: 457.
133. Cao YL, Lin JH, Hammes HP, Zhang C (2022) Flavonoids in Treatment of Chronic Kidney Disease. Molecules 27: 2365.
134. Liu J, Wang X, Yong H, Kan J, Jin C (2018) Recent advances in flavonoid-grafted polysaccharides: Synthesis, structural characterization, bioactivities and potential applications. Int J Biol Macromol 116: 1011-1025.
135. Yang N, Gao J, Hou R, Xu X, Yang N et al. (2021) Grape Seed Proanthocyanidins Inhibit Migration and Invasion of Bladder Cancer Cells by Reversing EMT through Suppression of TGF-β Signaling Pathway. Oxid Med Cell Longev 2021: 5564312.
136. Zhang Y , Chen S , Wei C , Rankin GO , Ye X et al. (2018) Dietary compound proanthocyanidins from Chinese bayberry (Myrica rubra Sieb. et Zucc.) leaves attenuate chemotherapy-resistant ovarian cancer stem cell traits via targeting the Wnt/β-catenin signaling pathway and inducing G1 cell cycle arrest. Food Funct 9: 525-533.
137. Giordano A, Tommonaro G (2019) Curcumin and Cancer. Nutrients 11: 2376.
138. Trujillo J, Granados Castro LF, Zazueta C, Andérica Romero AC, Chirino YI et al. (2014) Mitochondria as a target in the therapeutic properties of curcumin. Arch Pharm (Weinheim) 347: 873-884.
139. Unlu A, Nayir E, Dogukan Kalenderoglu M, Kirca O, Ozdogan M (2016) Curcumin (Turmeric) and cancer. J BUON 21: 1050-1060.
140. Wang G, Duan P, Wei Z, Liu F (2022) Curcumin sensitizes carboplatin treatment in triple negative breast cancer through reactive oxygen species induced DNA repair pathway. Mol Biol Rep 49: 3259-3270.
141. Begum N, Hockman S, Manganiello VC (2011) Phosphodiesterase 3A (PDE3A) deletion suppresses proliferation of cultured murine vascular smooth muscle cells (VSMCs) via inhibition of mitogen-activated protein kinase (MAPK) signaling and alterations in critical cell cycle regulatory proteins. J Biol Chem 286: 26238-262349.
142. Begum N, Shen W, Manganiello V (2011) Role of PDE3A in regulation of cell cycle progression in mouse vascular smooth muscle cells and oocytes: implications in cardiovascular diseases and infertility. Curr Opin Pharmacol 11: 725-729.
143. Shen W, Ahmad F, Hockman S, Ma J, Omi H et al. (2010) Female infertility in PDE3A(-/-) mice: polo-like kinase 1 (Plk1) may be a target of protein kinase A (PKA) and involved in meiotic arrest of oocytes from PDE3A(-/-) mice. Cell Cycle 9: 4720-4734.
144. Chapa Oliver AM, Mejía Teniente L (2016) Capsaicin: From Plants to a Cancer-Suppressing Agent. Molecules 21: 931.
145. Clark R, Lee SH (2016) Anticancer Properties of Capsaicin Against Human Cancer. Anticancer Res 36: 837-843.
146. Ravindranathan P, Pasham D, Balaji U, Cardenas J, Gu J et al. (2018) A combination of curcumin and oligomeric proanthocyanidins offer superior anti-tumorigenic properties in colorectal cancer. Sci Rep 8: 13869.
147. Toden S, Ravindranathan P, Gu J, Cardenas J, Yuchang M et al. (2018) Oligomeric proanthocyanidins (OPCs) target cancer stem-like cells and suppress tumor organoid formation in colorectal cancer. Sci Rep 8: 3335.
148. Viale PH (2020)The American Cancer Society's Facts & Figures: 2020 Edition. J Adv Pract Oncol 11: 135-136.
149. Parisi A, Porzio G, Pulcini F, Cannita K, Ficorella C et al. (2021) What Is Known about Theragnostic Strategies in Colorectal Cancer. Biomedicines 9: 140.
150. Nalluri H, Subramanian S, Staley C (2020) Intestinal organoids: a model to study the role of microbiota in the colonic tumor microenvironment. Future Microbiol 15: 1583-1594.
151. Barbáchano A, Fernández Barral A, Bustamante Madrid P, Prieto I, Rodríguez Salas N et al. (2021) Organoids and Colorectal Cancer. Cancers (Basel) 13: 2657.
152. Schutgens F, Clevers H (2020) Human Organoids: Tools for Understanding Biology and Treating Diseases. Annu Rev Pathol 15: 211-234.
153. Needham BD, Funabashi M, Adame MD, Wang Z, Boktor JC et al. (2022) A gut-derived metabolite alters brain activity and anxiety behaviour in mice. Nature 602: 647-653.
154. Liu Z, Ma A, Mathé E, Merling M, Ma Q et al. (2021) Liu B. Network analyses in microbiome based on high-throughput multi-omics data. Brief Bioinform 22: 1639-1655.
155. Franzosa EA, Hsu T, Sirota Madi A, Shafquat A, Abu Ali G et al. (2015) Sequencing and beyond: integrating molecular 'omics' for microbial community profiling. Nat Rev Microbiol 13: 360-372.
156. Aw W, Fukuda S (2018) Understanding the role of the gut ecosystem in diabetes mellitus. J Diabetes Investig 9: 5-12.
157. Lamichhane S, Sen P, Dickens AM, Orešič M, Bertram HC (2018) Gut metabolome meets microbiome: A methodological perspective to understand the relationship between host and microbe. Methods 149: 3-12.
158. Tsiantas K, Konteles SJ, Kritsi E, Sinanoglou VJ, Tsiaka T et al. (2022) Effects of Non-Polar Dietary and Endogenous Lipids on Gut Microbiota Alterations: The Role of Lipidomics. Int J Mol Sci 23: 4070.
159. Wang X, Gibson GR, Costabile A, Sailer M, Theis S et al. (2019) Prebiotic Supplementation of In Vitro Fecal Fermentations Inhibits Proteolysis by Gut Bacteria, and Host Diet Shapes Gut Bacterial Metabolism and Response to Intervention. Appl Environ Microbiol 85: e02749-e02718.
160. Ashaolu TJ, Ashaolu JO (2021) Prebiotic peptides, their formation, fermentation in the gut, and health implications. Biotechnol Prog 37: e3142.
161. Larder CE, Iskandar MM, Kubow S (2021) Gastrointestinal Digestion Model Assessment of Peptide Diversity and Microbial Fermentation Products of Collagen Hydrolysates. Nutrients 13: 2720.
162. Ratajczak W, Mizerski A, Rył A, Słojewski M, Sipak O et al. (2021) Alterations in fecal short chain fatty acids (SCFAs) and branched short-chain fatty acids (BCFAs) in men with benign prostatic hyperplasia (BPH) and metabolic syndrome (MetS). Aging (Albany NY)13: 10934-10954.
163. Silva YP, Bernardi A, Frozza RL (2020) The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne) 11: 25.
164. Li C, Liang Y, Qiao Y (2022) Messengers From the Gut: Gut Microbiota-Derived Metabolites on Host Regulation. Front Microbiol 13: 863407.
165. Tsuchida S, Nakayama T (2022) Metabolomics Research in Periodontal Disease by Mass Spectrometry. Molecules 27: 2864.
166. Yang H, Wang Z, Shi S, Yu Q, Liu M et al. (2022) Identification of cerebrospinal fluid metabolites as biomarkers for neurobrucellosis by liquid chromatography-mass spectrometry approach. Bioengineered 13: 6996-7010.

167. Bozzetti V, Senger S (2022) Organoid technologies for the study of intestinal microbiota-host interactions. Trends Mol Med 28: 290-303.
168. Williamson IA, Arnold JW, Samsa LA, Gaynor L, DiSalvo M, et al. (2018) A High-Throughput Organoid Microinjection Platform to Study Gastrointestinal Microbiota and Luminal Physiology. Cell Mol Gastroenterol Hepatol 6: 301-319.
169. Sim JR, Kang SS, Lee D, Yun CH, Han SH (2018) Killed Whole-Cell Oral Cholera Vaccine Induces CCL20 Secretion by Human Intestinal Epithelial Cells in the Presence of the Short-Chain Fatty Acid, Butyrate. Front Immunol 9: 55.
170. Wang RX, Lee JS, Campbell EL, Colgan SP (2020) Microbiota-derived butyrate dynamically regulates intestinal homeostasis through regulation of actin-associated protein synaptopodin. Proc Natl Acad Sci U S A 117: 11648-11657.
171. Wang T, Rijnaarts I, Hermes GDA, de Roos NM, Witteman BJM et al. (2022) Fecal Microbiota Signatures Are Not Consistently Related to Symptom Severity in Irritable Bowel Syndrome. Dig Dis Sci 67: 5137-5148.
172. Ridaura V, Belkaid Y (2015) Gut microbiota: the link to your second brain. Cell 161: 193-194.
173. Reigstad CS, Salmonson CE, Rainey JF 3rd, Szurszewski JH, Linden DRet al. (2015) Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB J 29: 1395-1403.
174. Wanders RJ, Waterham HR, Ferdinandusse S (2016) Metabolic Interplay between Peroxisomes and Other Subcellular Organelles Including Mitochondria and the Endoplasmic Reticulum. Front Cell Dev Biol 3: 83.
175. Beumer J, Clevers H (2017) How the Gut Feels, Smells, and Talks. Cell 170: 10-11.
176. Li Y, Hao Y, Zhu J, Owyang C (2000) Serotonin released from intestinal enterochromaffin cells mediates luminal non-cholecystokinin-stimulated pancreatic secretion in rats. Gastroenterology 118:1197-1207.
177. Ko M, Kamimura K, Owaki T, Nagoya T, Sakai N et al. (2021) Modulation of serotonin in the gut-liver neural axis ameliorates the fatty and fibrotic changes in non-alcoholic fatty liver. Dis Model Mech 14: dmm048922.
178. Cacabelos R, Naidoo V, Corzo L, Cacabelos N, Carril JC (2021) Genophenotypic Factors and Pharmacogenomics in Adverse Drug Reactions. Int J Mol Sci 22: 13302.
179. Siwczak F, Loffet E, Kaminska M, Koceva H, Mahe MM et al. (2021) Intestinal Stem Cell-on-Chip to Study Human Host-Microbiota Interaction. Front Immunol 12: 798552.
180. Sommer F, Bäckhed F (2016) Know your neighbor: Microbiota and host epithelial cells interact locally to control intestinal function and physiology. Bioessays 38: 455-464.
181. Chen C, Chen L, Lin L, Jin D, Du Yet al. (2021) Research progress on gut microbiota in patients with gastric cancer, esophageal cancer, and small intestine cancer. Appl Microbiol Biotechnol 105: 4415-4425.
182. Grzymajlo K (2022) The Game for Three: Salmonella-Host-Microbiota Interaction Models. Front Microbiol 13: 854112.
183. Mather AE, Reid SW, Maskell DJ, Parkhill J, Fookes MC et al. (2013) Distinguishable epidemics of multidrug-resistant Salmonella Typhimurium DT104 in different hosts. Science 341: 1514-1517.
184. Espinal A, Epperly MW, Mukherjee A, Fisher R, Shields D et al. (2022) Intestinal Radiation Protection and Mitigation by Second-Generation Probiotic Lactobacillus-reuteri Engineered to Deliver Interleukin-22. Int J Mol Sci 23: 5616.
185. Wang X, Liu Y, Wu Z, Zhang P, Zhang X (2022) Tea Polyphenols: A Natural Antioxidant Regulates Gut Flora to Protect the Intestinal Mucosa and Prevent Chronic Diseases. Antioxidants (Basel) 11: 253.
186. Sun Q, Cheng L, Zhang X, Wu Z, Weng P (2021) The interaction between tea polyphenols and host intestinal microorganisms: an effective way to prevent psychiatric disorders. Food Funct 12: 952-962.
187. Co JY, Margalef Català M, Li X, Mah AT, Kuo CJ et al. (2019) Controlling Epithelial Polarity: A Human Enteroid Model for Host-Pathogen Interactions. Cell Rep 26: 2509-2520.
188. Cardenas D, Bhalchandra S, Lamisere H, Chen Y, Zeng XL et al. (2020) Two- and Three-Dimensional Bioengineered Human Intestinal Tissue Models for Cryptosporidium. Methods Mol Biol 2052: 373-402.
189. Blutt SE (2018) The Next MacGyver: A Platform to Study Intestinal Organoids Using High-Throughput Computer-Driven Microinjection. Cell Mol Gastroenterol Hepatol 6: 352-353.
190. Dheer R, Young VB (2021) Stem-cell-derived models: tools for studying role of microbiota in intestinal homeostasis and disease. Curr Opin Gastroenterol 37: 15-22.
191. Moysidou CM, Owens RM (2021) Advances in modelling the human microbiome-gut-brain axis in vitro. Biochem Soc Trans 49: 187-201.
192. Azar J, Bahmad HF, Daher D, Moubarak MM, Hadadeh O et al. (2021) The Use of Stem Cell-Derived Organoids in Disease Modeling: An Update. Int J Mol Sci 22: 7667.
193. Grzymajlo K (2022) The Game for Three: Salmonella-Host-Microbiota Interaction Models. Front Microbiol 13: 854112.
194. Brouwer Brolsma EM, Brennan L, Drevon CA, van Kranen H, Manach C et al. (2017) Combining traditional dietary assessment methods with novel metabolomics techniques: present efforts by the Food Biomarker Alliance. Proc Nutr Soc 76: 619-627.
195. Crowder SL, Playdon MC, Gudenkauf LM, Ose J, Gigic B et al. (2022) A Molecular Approach to Understanding the Role of Diet in Cancer-Related Fatigue: Challenges and Future Opportunities. Nutrients 14: 1496.
196. Sayed IM, El Hafeez AAA, Maity PP, Das S, Ghosh P (2021) Modeling colorectal cancers using multidimensional organoids. Adv Cancer Res 151: 345-383.
197. Jin MZ, Han RR, Qiu GZ, Ju XC, Lou G et al. (2018) Organoids: An intermediate modeling platform in precision oncology. Cancer Lett 414: 174-180.
198. Xia X, Li F, He J, Aji R, Gao D (2019) Organoid technology in cancer precision medicine. Cancer Lett 457: 20-27.
199. Zhang R, Guo T, Ji L, Yin Y, Feng S et al. (2021) Development and Application of Patient-Derived Cancer Organoidsin Clinical Management of Gastrointestinal Cancer: A State-of-the-Art Review. Front Oncol 11: 716339.
200. Pinho D, Santos D, Vila A, Carvalho S (2021) Establishment of Colorectal Cancer Organoids in Microfluidic-Based System. Micromachines (Basel) 12: 497.
201. Shrestha B (2020) Single-Cell Metabolomics by Mass Spectrometry. Methods Mol Biol 2064: 1-8.
202. Blaser MC, Kraler S, Lüscher TF, Aikawa E (2021) Multi-Omics Approaches to Define Calcific Aortic Valve Disease Pathogenesis. Circ Res 128: 1371-1397.
203. Shrestha B (2020) Ten Major Future Challenges in Single-Cell Metabolomics. Methods Mol Biol 2064: 219-223.
204. Bačenková D, Trebuňová M, Čížková D, Hudák R, Dosedla E et al. (2022) In Vitro Model of Human Trophoblast in

Early Placentation. Biomedicines 10: 904.

205. Bossel Ben Moshe N, Hen Avivi S, Levitin N, Yehezkel D, Oosting M et al. (2019) Predicting bacterial infection outcomes using single cell RNA-sequencing analysis of human immune cells. Nat Commun 10: 3266.
206. Hwang B, Lee JH, Bang D (2021) Single-cell RNA sequencing technologies and bioinformatics pipelines. Exp Mol Med 50: 1-14.
207. Xie J, Chen L, Sun Q, Li H, Wei W et al. (2022) An immune subtype-related prognostic signature of hepatocellular carcinoma based on single-cell sequencing analysis. Aging (Albany NY) 14: 3276-3292.
208. Laschke MW, Menger MD (2017) Life is 3D: Boosting Spheroid Function for Tissue Engineering. Trends Biotechnol 35: 133-144.
209. Hong X, Fu J, Liu Y, Li S, Wang X et al. (2019) Recent Progress on Graphene/Polyaniline Composites for High-performance Supercapacitors. Materials (Basel) 12: 1451.
210. Gavane V, Koulgi S, Jani V, Uppuladinne MVN, Sonavane U et al. (2019) TANGO: A high through-put conformation generation and semiempirical method-based optimization tool for ligand molecules. J Comput Chem 40: 900-909.
211. Singh RP, Bashir H, Kumar R (2021) Emerging role of microbiota in immunomodulation and cancer immunotherapy. Semin Cancer Biol 70: 37-52.
212. Sholl J, Sepich Poore GD, Knight R, Pradeu T (2022) Redrawing therapeutic boundaries: microbiota and cancer. Trends Cancer 8: 87-97.
213. Zinöcker MK, Lindseth IA. (2018) The Western Diet-Microbiome-Host Interaction and Its Role in Metabolic Disease. Nutrients 10: 365.
214. Capozzi F (2022) Food Innovation in the Frame of Circular Economy by Designing Ultra-Processed Foods Optimized for Sustainable Nutrition. Front Nutr 9: 886220.
215. Martinez KB, Leone V, Chang EB (2017) Western diets, gut dysbiosis, and metabolic diseases: Are they linked? Gut Microbes 8: 130-142.
216. Wu L, Xie X, Liang T, Ma J, Yang L et al. (2021) Integrated Multi-Omics for Novel Aging Biomarkers and Antiaging Targets. Biomolecules 12: 39.
217. Sun YV, Hu YJ (2016) Integrative Analysis of Multi-omics Data for Discovery and Functional Studies of Complex Human Diseases. Adv Genet 93: 147-190.
218. Jin Z, Zhang JD, Wu X, Cao G (2019) Metabolomics study of the therapeutic mechanism of a Chinese herbal formula on collagen-induced arthritis mice. RSC Adv 9: 3716-3725.
219. Akiyama M (2021) Multi-omics study for interpretation of genome-wide association study. J Hum Genet 66: 3-10.
220. Read MN, Holmes AJ (2017) Towards an Integrative Understanding of Diet-Host-Gut Microbiome Interactions. Front Immunol 8: 538.
221. Schewe M, Sacchetti A, Schmitt M, Fodde R (2017) The Organoid Reconstitution Assay (ORA) for the Functional Analysis of Intestinal Stem and Niche Cells. J Vis Exp 129: 56329.
222. Drobny A, Ngo PA, Neurath MF, Zunke F, López Posadas R (2021) Molecular Communication Between Neuronal Networks and Intestinal Epithelial Cells in Gut Inflammation and Parkinson's Disease. Front Med (Lausanne) 8: 655123.
223. Aguirre Garcia M, Hillion K, Cappelier JM, Neunlist M, Mahe MM et al. (2022) Intestinal Organoids: New Tools to Comprehend the Virulence of Bacterial Foodborne Pathogens. Foods 11: 108.
224. Mercadante V, Scarpa E, De Matteis V, Rizzello L, Poma A (2021) Engineering Polymeric Nanosystems against Oral Diseases. Molecules 26: 2229.
225. Nitsche KS, Müller I, Malcomber S, Carmichael PL, Bouwmeester H (2022) Implementing organ-on-chip in a next-generation risk assessment of chemicals: a review. Arch Toxicol 96: 711-741.
226. Murrow LM, Weber RJ, Gartner ZJ (2017) Dissecting the stem cell niche with organoid models: an engineering-based approach. Development 144: 998-1007.
227. Kim W, Gwon Y, Park S, Kim H, Kim J (2022) Therapeutic strategies of three-dimensional stem cell spheroids and organoids for tissue repair and regeneration. Bioact Mater 19: 50-74.
228. Ong CS, Zhou X, Han J, Huang CY, Nashed A et al. (2018) In vivo therapeutic applications of cell spheroids. Biotechnol Adv 36: 494-505.
229. Ivascu A, Kubbies M (2006) Rapid generation of single-tumor spheroids for high-throughput cell function and toxicity analysis. J Biomol Screen 11: 922-932.
230. Zhuang P, Chiang YH, Fernanda MS, He M (2021) Using Spheroids as Building Blocks Towards 3D Bioprinting of Tumor Microenvironment. Int J Bioprint 7: 444.
231. Okada S, Vaeteewoottacharn K, Kariya R (2018) Establishment of a Patient-Derived Tumor Xenograft Model and Application for Precision Cancer Medicine. Chem Pharm Bull (Tokyo) 66: 225-230.
232. Yin Z, Maswikiti EP, Liu Q, Bai Y, Li X et al. (2021) Current research developments of patient-derived tumour xenograft models (Review). Exp Ther Med 22: 1206.
233. Lee JW, Sung JS, Park YS, Chung S, Kim YH (2018) Isolation of spheroid-forming single cells from gastric cancer cell lines: enrichment of cancer stem-like cells. Biotechniques 65: 197-203.
234. Perez Muñoz ME, Sugden S, Harmsen HJM, 't Hart BA, Laman JD et al. (2021) Nutritional and ecological perspectives of the interrelationships between diet and the gut microbiome in multiple sclerosis: Insights from marmosets. iScience 24: 102709.
235. Hsu CK, Su SC, Chang LC, Shao SC, Yang KJ et al. (2021) Effects of Low Protein Diet on Modulating Gut Microbiota in Patients with Chronic Kidney Disease: A Systematic Review and Meta-analysis of International Studies. Int J Med Sci 18: 3839-3850.
236. Janney A, Powrie F, Mann EH (2020) Host-microbiota maladaptation in colorectal cancer. Nature 585: 509-517.
237. Pradhan S, Weiss AA (2020) Probiotic Properties of Escherichia coli Nissle in Human Intestinal Organoids. mBio 11: e01470-20.
238. Clevers H (2016) Modeling Development and Disease with Organoids. Cell 165: 1586-1597.
239. Ho BX, Pek NMQ, Soh BS (2018) Disease Modeling Using 3D Organoids Derived from Human Induced Pluripotent Stem Cells. Int J Mol Sci 19: 936.
240. Chattopadhyay I, Gundamaraju R, Jha NK, Gupta PK, Dey A et al . (2022) Interplay between Dysbiosis of Gut Microbiome, Lipid Metabolism, and Tumorigenesis: Can Gut Dysbiosis Stand as a Prognostic Marker in Cancer? Dis Markers 2022: 2941248.
241. Katsaounou K, Nicolaou E, Vogazianos P, Brown C, Stavrou M et al. (2022) Colon Cancer: From Epidemiology to Prevention. Metabolites 12: 499.
242. Yu Y, Cai Y, Yang B, Xie S, Shen W et al. (2022) High-Fat Diet Enhances the Liver Metastasis Potential of Colorectal Cancer through Microbiota Dysbiosis. Cancers (Basel)

14: 2573.

243. Liu J, Zhang Y (2022) Intratumor microbiome in cancer progression: current developments, challenges and future trends. Biomark Res 10: 37.
244. Suga D, Mizutani H, Fukui S, Kobayashi M, Shimada Y et al. (2022) The gut microbiota composition in patients with right- and left-sided colorectal cancer and after curative colectomy, as analyzed by 16S rRNA gene amplicon sequencing. BMC Gastroenterol 22: 313.
245. Winiarska Mieczan A, Tomaszewska E, Donaldson J, Jachimowicz K (2022) The Role of Nutritional Factors in the Modulation of the Composition of the Gut Microbiota in People with Autoimmune Diabetes. Nutrients 14: 2498.
246. Yao N, Yang Y, Li X, Wang Y, Guo R et al. (2022) Effects of Dietary Nutrients on Fatty Liver Disease Associated With Metabolic Dysfunction (MAFLD): Based on the Intestinal-Hepatic Axis. Front Nutr 9: 906511.
247. Bouyahya A, Omari NE, El Hachlafi N, Jemly ME, Hakkour M et al. (2022) Chemical Compounds of Berry-Derived Polyphenols and Their Effects on Gut Microbiota, Inflammation, and Cancer. Molecules 27: 3286.
248. Koulouris A, Tsagkaris C, Messaritakis I, Gouvas N, Sfakianaki M et al. (2021) Resectable Colorectal Cancer: Current Perceptions on the Correlation of Recurrence Risk, Microbiota and Detection of Genetic Mutations in Liquid Biopsies. Cancers (Basel) 13: 3522.
249. (2020) Abstracts from the 53rd European Society of Human Genetics (ESHG) Conference: Interactive e-Posters. Eur J Hum Genet 28: 141-797
250. Comte B, Baumbach J, Benis A, Basílio J, Debeljak N et al. (2020) Network and Systems Medicine: Position Paper of the European Collaboration on Science and Technology Action on Open Multiscale Systems Medicine. Netw Syst Med 3: 67-90.
251. Zhao A, Jeffery EH, Miller MJ (2022) Is Bitterness Only a Taste? The Expanding Area of Health Benefits of Brassica Vegetables and Potential for Bitter Taste Receptors to Support Health Benefits. Nutrients 14: 1434.
252. Augimeri G, Montalto FI, Giordano C, Barone I, Lanzino M et al. (2021) Nutraceuticals in the Mediterranean Diet: Potential Avenues for Breast Cancer Treatment. Nutrients 13: 2557.
253. Alam W, Ullah H, Santarcangelo C, Di Minno A, Khan H et al. (2021) Micronutrient Food Supplements in Patients with Gastro-Intestinal and Hepatic Cancers. Int J Mol Sci 22: 8014.
254. Porro C, La Torre ME, Tartaglia N, Benameur T, Santini M et al. (2022) The Potential Role of Nutrition in Lung Cancer Establishment and Progression. Life (Basel) 12: 270.
255. Tümkaya Yılmaz S, Malfliet A, Elma Ö, Deliens T, Nijs J et al. (2022) Diet/Nutrition: Ready to Transition from a Cancer Recurrence/Prevention Strategy to a Chronic Pain Management Modality for Cancer Survivors? J Clin Med 11: 653.