



A Potential Role of Xenometabolites as Nutraceutical: A Concurrent Review

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Abstract

The gut microbiota has the capacity to de-novo manufacture or change endogenous and exogenous substances to produce or alter xenometabolites (i.e., non-host-derived metabolites). A wide-scale characterization of these metabolites is still lacking, despite rare instances of xenometabolites impacting host health and illness. Numerous studies have been conducted to investigate how the gut microbiome affects individual function and health, including links between specific intestinal microorganism populations and metabolites and the health of the systemic-immune system and gastrointestinal tract. The current review article delves into the sources of xenometabolites and the role of modeling in addressing the complexity of the xenometabolites process, as well as various nutraceutical benefits such as antibiotics, anti-tumor, and anti-cancer action.



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Introduction


Although orally ingested xenometabolites (small compounds originating from natural products, foods, medicines, and industrial origins) have been significantly discovered, microbe-generated xenometabolites have received less attention. It is becoming increasingly clear that the intestinal flora impacts host health and illness.¹ The role of

microbially formed xenometabolites, or bacterial transformation of moderator metabolites, to moderator physiology is well substantiated by the available information.² It has been revealed that colonic epithelial cells' synthesis of butyrate stimulates -oxidation and promotes the proliferation of intestinal regulatory T cells, establishing a positive response loop that keeps the intestinal

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epithelia and obligatory anaerobes in a mutually favorable relationship.³ On top of the straight effects on intestinal tissues, several reports have recommended a link between microbe-derived xenometabolites and heart disease⁴ and several other diseases.⁵ Metabolomics has been a primary tool to recognize target tissues for some microbe-derived xenometabolites in various host tissues.⁶ However, on-guard evaluation of assumed xenometabolite formation, absorption, shipment, and interorgan flux has never been conducted. The objective of the recent study was to characterize the roots and potential organ objectives of alleged xenometabolites and microbe-modified metabolic products in good shape post-absorptive awake pigs using a specialized metabolomics framework (XenoScan) nourished in xenometabolites, their variants, and gastrointestinal (GI)-related substances (bile acids). Following investigation employed the XenoScan living up on the library of real standards from the Arkansas Children's Nutrition Center and centered on known and speculative xenometabolites and their variants.⁷ Maximum range were produced for all the metabolites in our internal collection (i.e., unrestricted to only microbial commodified metabolites and xenometabolites). The biggest outer layer of microbial contact with the human defense system is made up by intestinal commensals, or the gut microbiota, which outnumber human body cells. This dynamic interface, which is made up of several metabolic, immune, and provocative responses, survive in a precarious stability between disease and symbiosis and could affect a variety of physiological features of the host. High-throughput arrangement, metabolite characterization, and bioinformatics data are modifying our information of the relationships of the stomach microbiota remoter, despite accumulating confirmation that the digestive system microbiome has a significant part in carcinogenesis.⁸ The investigation of the footprint of microbiota on medication placement, undertaking, and dreadfulness, or "pharmacomicrobiomics," in particular, is highlighting the vital role that microbes play in the effectiveness and toxic effect of treatment for cancer.⁹ By modifying host-chemotherapeutic-microbiota interplay and personalizing chemotherapy procedure depending on an assessment of the bacterial habitat of a person (the genetic makeup of their microorganisms), pharmacomicrobiomics has the potential to improve curative order and eliminate harmful effects.¹⁰ A deeper comprehension of the

tangled interactions between the immune system and the gut bacteria may set about the evolution of a new chemotherapeutic plan of action.¹¹

Xenometabolites

It is believed that xenometabolites derived from plant and microbial sources have both helpful and harmful impacts on host physiology. There are few studies examining xenometabolite tissue uptake and absorption. Kelly *et al.*¹² assessed the interorgan flow of elucidated familiar and putative xenometabolites, derivative products, and blistering acids in a mindful catheterized pig model. It has been demonstrated that the bacteria in the digestive tract may alter or metabolize various xenobiotics, including modern cancer medications, millennia-old analgesics, and food supplements.¹³ Recent investigation has also revealed the viability of utilizing and modifying such a microbe-mediated xenometabolism to enhance host health or prevent adverse drug reactions. For instance, Wallace *et al.*¹⁴ shown that blocking bacterial b-glucuronidase can prevent a harmful bioconversion of the cancer medication irinotecan. Probiotic bacteria, such as *Lactobacillus sp.*, have been demonstrated to alleviate diarrhea, illnesses linked to *Clostridium difficile*, and other antibiotic adverse effects.¹⁵ Although few workrooms have devoted genuine quality athenaeum that cover the broad range of substances involved in metabolism caused by bacterial activity, metabolomics has proven highly useful in identifying molecular assay of microbial metabolism. Identification of microbial-specific metabolites is further complicated by the fact that the majority of large-scale metabolomics instruments use basic and spectroscopic libraries that often include human and animal metabolic pathways. To solve this problem, a metabolomics manifesto was created that allows for a stronger focal point on "nonhost" xenometabolites, xenometabolite variants, cometabolites, & congeners. This platform may be used to better analyze changes in the microbial environment. Because of developments in omics technology, the molecular routes of xenometabolism inside the intestinal microbiota have now begun to emerge through the recognition of the microbes and enzymes in charge.¹⁶ Today, a significant fragment of the bacterial species colonising the human gut can be identified with the aid of metagenomics tools.¹⁷ Additionally, these tools are illuminating the gut microbiome's genetic repertoire in an unprecedented level of detail.

Sources of Xenometabolites

The primary biopolymeric component of plants, starch, which includes kernels, nut, and radix, appears in distinctive sandy forms in a variety of sizes and structures.¹⁸⁻¹⁹ The main medium of physiological energy found in the human food is starch, which is why it is generally categorized as a readily accessible carbohydrate. Nutritionists & food technologists especially have been interested in the importance of starch as a functional polysaccharide. Both the food and non-food sectors use starch in a wide range of products. In addition to providing calories, starch is also found major part in the texture of food, which affects its organoleptic qualities. This is true of most processed food systems. Dietary fibre (DF) is basically made up of outer covering of plant constituents like polysaccharides and lignin and is commonly described as the large molecules in the food that withstand breakdown by human inner enzymes. In the past 20 years, DF has significantly lowered the risk of a wide range of illnesses, including diabetes mellitus, heart conditions, cancer of large intestine, constipation, and diverticulosis. High-fibre diets have slowed nutrient uptake, increased fecal volume, decreased blood lipids, reduced risk of cancer of the large intestine, an obstacle to breakdown, mobile intestinal parts, longer fecal elimination times, and properties that are fermentable. The multiple positive physiological impacts of DF and how they relate to how the

large and small intestines operate.²⁰ Dietary fibre is a mixture of structurally diverse components such cellulose, hemicelluloses, pectic substances, gums, mucilages, complex carbohydrates, other polysaccharides, and lignin, a non-carbohydrate polymer made of phenyl propane remainings, rather than making up a specific chemical group. DF is primarily divided into two further forms: soluble DF and insoluble DF. Most research on the interactions among the bacteria of digestive tract and the host has concentrated on relations among the fullness of particular microbes and particular (patho) physiological variables, allowing for the formation of hypotheses concerning the possible bacterial taxa that may be tangled. When combined with the vast biomass of microorganisms in the intestinal system and the complex chemical mixes in food, the gut microbiome has a great genetic makeup (number of gene variants and genes) that has a significant nonenzymatic and enzymatic capacity for producing xenometabolites. De novo formation, bacterial transformation of external parts (such as phytochemicals, fibres, oligosaccharides, pharmaceutical compounds, etc.), and bacterial alternation of molecules originating from hosts can all be used to achieve this (central bile acids, urea, etc.). Due to the fact that both the host and the microbe are involved in their metabolism, the latter are also known as "cometabolites" (s).²¹⁻²²

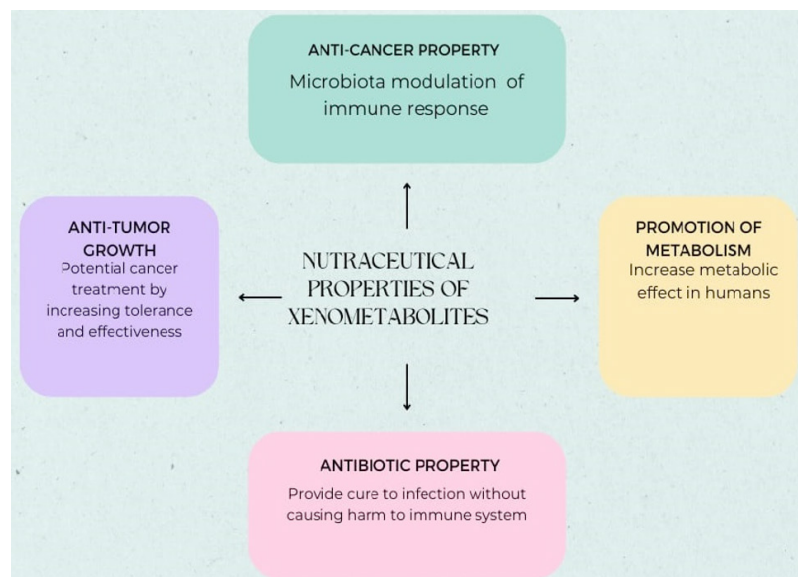


Fig. 1: Depicts nutraceutical properties of xenometabolites

Role of Modeling In Tackling Complexity of Xenometabolic Processes

Because of three key factors—the broad license of metabolic enzymes, the constructional diversity of the bacteria presents in digestive track, as well as the interconnections among the recipient and the microbe-mediated xenometabolism—xenometabolic activities in the gut can be extremely complicated. According to Tawfik,²³ the versatility of metabolic enzymes increases the number of potential pathways by which a xenobiotic chemical could be digested or changed when combined with the microbiota's enzymatic reserve. This complexity is further increased by the host-microbiota interactivity during the enterohepatic cycle, the textural variety and natural variability of the microbiota, and other factors. The appeal for modeling and simulation of xenometabolism is increased by these inherent complexities and the limitations in collecting *in vivo* studies from human participants. A comprehensive modeling framework that considers coupled host-microbiota xenometabolism might be useful for developing drugs and developing individualised medication plans. A platform like this would make it possible to forecast probable xenometabolic pathways and so create provable hypotheses. In spite of the fact that no manifesto now addresses all of the many difficulties during modeling xenometabolism, there are a number of technologies that can handle the crucial individual phases. These methods include modeling biochemical interactions in microbial populations and forecasting enzyme-level bioconversion.²⁴⁻²⁵ Here, discuss these various tools and outline the key ideas that guide how they operate and also provide a number of xenometabolism examples and talk about how computational techniques that focus on various xenometabolic processes may be merged into a unified platform.

Anti-Cancerous Property

Chemotherapeutic response is significantly influenced by the microbiota's modulation of the immune response. It has been demonstrated that continual communication between the immune system's innate and adaptive responses and gut bacteria at the mucosal surface controls inflammation and sets the immunological tone.²⁶ Chemotherapeutic drugs may cause mucosal epithelial destruction, which may lead to bacterial translocation. Greater exposure to harmful microorganisms may result

in systemic infection, but it can also stimulate the adaptive immune responses, enhancing the host's response to chemotherapy.²⁷ There are several different ways that immunomodulation can happen. Bacterial translocation, T-helper 17 cell activation, intraluminal myeloid cell activation, and microbiota-driven T-cell activation are crucial in aiding new anti-cancer immunotherapy.²⁸ Cyclophosphamide is made more effective by these factors as well as by oxaliplatin.

Anti-tumour Growth

Sivan *et al.*²⁹ found that genetically comparable mice from two parties Farms (Tac) and Jackson Laboratory—grew melanoma differently (Jax). When compared to Jax mice, Tac animals had more aggressive tumor growth, which could be reversed by co-housing or colonic transfer by Jax mice. The reverse fecal transfer did not result in accelerated tumor development. Additionally, Tac mice had a reduced ability to respond to the chemotherapy drug anti-programmed necrosis 1 ligand-1 monoclonal antibodies (anti-PD-L1, pembrolizumab) as compared to Jax animals. The existence of *Bifidobacterium* spp. in the intestinal flora of Jax mice was found to be responsible for the reduced basal cancer progression and improved anti-cancer response to anti-PD-L1. These bacteria are thought to cooperate with dendritic cells to stimulate T cells and enhance a shielding anti-cancer response. *Bifidobacterium* spp. management to Tac mice was able to delay the formation of basal tumors to improve the anti-tumor impact of anti-PD-L1.²⁹ In addition to promoting intestinal flora and anti-tumor responses, the gut microbiota also induces chronic dysregulated inflammation, which has genotoxic consequences and can cause carcinogenesis.³⁰ The makeup of the gut bacteria and the equilibrium between hazardous microbial population within the microbiome ultimately determine if the gut bacteria will promote colon cancer or create a healthy symbiotic connection with the host. It is unknown, nevertheless, if this "dysbiosis" might precede or lead to colorectal cancer (CRC). Studies on mice overwhelmingly support the idea that the gut microbiota may influence CRC susceptibility and may be used as early diagnostic indicators as well as treatment targets. Such clinical studies must to take into account the impact of each person's race, way of life, food, material type, the position of the tissue collected, and the gut microbiome. There have been

a number of significant changes in the taxonomic levels in the gut bacteria ecology of CRC patients. In both the intestinal mucosa and the patients' feces, there is a rise in Bacteroides, Fusobacteria, as well as Proteobacteria and a reduction in Firmicutes.³¹ The three best known variants in colorectal carcinogenesis are enterotoxigenic strains of *B. fragilis*, polyketide synthase (PKS) positive variants of *E. coli*, and *Fusobacterium nucleatum*.³² The intestinal bacteria are a zestful shape that is affected by complicated interlinkage among several variables,

including host immunity, chemotherapeutics, concurrent medicines, environment, and food during cancer treatment.¹¹ Both therapeutic advantages and disadvantages might result from the microbiota's functional variety. It will need a committed and cutting-edge systems medicine approach to gain a thorough understanding of the purpose of the intestinal microbiota, including their role in chemotherapy. It is extremely difficult to manipulate the gut microbiota in a way that maximizes chemotherapy effectiveness while minimizing negative effects.³³

Table 1: Nutraceutical properties of xenometabolite

Metabolite process	Nutraceutical properties	Study	Reference
Xenometabolite (Complex biochemical process)	modeling of the intestinal flora liver biological change	study of microbes and enzymes	(34)
Xenometabolite Millennia	determining chemotherapeutic (cancerous) lung cancer	Human (study was conducted in 15 centers in six countries of Central and Eastern Europe)	(35, 36)
xenometabolite hubs	UC Davis Type 2 Diabetes Mellitus (UCD-T2DM)	Male rats	(7)
Xenometabolites dietary fiber	Detoxification Organs Improve liver (alter liver metabolism) and kidney (reduced indole cresol burden) function	animal models	(37)

Antibiotic Property

Numerous studies have examined (see Table 1) the links between antibiotic usage and chemotherapy effectiveness, but few have addressed the clear confirmation that microbiota dysbiosis brought on by antibiotic treatment increases the possibility of cancer. In breast cancer (BC) patients having febrile neutropenia (FN), a serious side effect brought on by chemotherapy, antibiotics are needed to prevent and cure harmful bacterial infections.³⁸ Different infections can be successfully treated with antibiotics. Intestinal dysbacteriosis results, however, since their use cannot be pinpointed as accurately as targeted medications. A growing body of evidence indicates that the gut microbiota affects the effectiveness of anti-tumor treatment, such as chemotherapy, immunotherapy, radiation treatment, and surgery, used to treat complex tumors (melanoma, lung

disease, and colorectal cancer). The gut microbiota plays a role in many aspects of human physiological functions, from generating nutrients and vitamins to combating pathogenic organisms and defending immune response advancement and outer covering mucosa equilibrium.³⁹

Contrary to specific pathogen-free (SPF) mice, antibiotic-tested mice exhibited oxaliplatin (OXA) chemoresistance in colon cancer and lymphoma, suggesting that antibiotic exposure was linked to decreased chemotherapy effectiveness.⁴⁰ The link between the impact of neoadjuvant treatment and antibiotics on BC requires more investigation. In BC patients with FN, a serious side effect of chemotherapy, antibiotics are needed to avert and cure infectious bacterial infections.³⁸ The use of antibiotics may be linked to decreased neoadjuvant

treatment effectiveness and a worse outcome in BC patients. The current study tried to assess how antibiotic administration affects the effectiveness and prognosis of neoadjuvant treatment in BC patients. Results anticipate serving as a foundation for future treatment ideas for BC patients who need antibiotics during neoadjuvant therapy.⁴¹ The cells that have xenometabolic competence identical to that which happens *in vivo* are the best at predicting human toxicity. This characteristic has a drawback in that detoxifying metabolism may cause cytotoxicity to be underestimated

Promotion of Metabolism

Metabolism is the process of generating energy by the breakdown of large molecules for the creation of desired molecules, large molecules include fats, carbohydrates and proteins, paired by minerals and vitamins as well. cytochrome P450 oxidases, UDP-glucuronosyltransferases, and glutathione "S"-transferases metabolise xenometabolites in human beings. There are three phases of enzyme action: prime step is to oxidize the xenobiotic (phase I) and then attach water-soluble groups onto the molecule (phase II). The molecules from phase II that are water-soluble are then pumped out of cells and in multicellular organisms may be further metabolized before being excreted (phase III). Novel plasma metabolite work action reflective of enhanced metabolic health (insulin sensitivity, fitness, reduced body weight) were caught into sight before and after a 14–17week weight loss and exercise intervention in sedentary, obese insulin-resistant women. To have check and balance on potential visibal effects of diet- or microbiome-derived molecules on the systemic metabolome, sampling was during a tightly-controlled feeding test week paradigm. Intervention- and insulin-sensitivity associated were revealed by Pairwise and multivariate analysis: (1) Changes in plasma xeno-metabolites ("non-self" metabolites of dietary or intestinal microbial origin) following an oral glucose tolerance test (e.g., higher post-OGTT propane-1,2,3-tricarboxylate [tricarballic acid]) or in the overnight-fasted state (e.g., lower γ -tocopherol)⁴²; Enhanced indices of saturated of appreciably-long chain fatty acid elongation capacity.⁴⁴³

Conclusion

The gut microbiota is rapidly becoming recognized as an important location of pharmaceutical and other

xenobiotic chemical metabolism important to human health. Although orally ingested xenometabolites (small compounds originating from natural products, foods, medicines, and industrial origins) have been significantly discovered, microbe-generated xenometabolites have received less attention. A growing body of evidence indicates that the gut microbiota affects the effectiveness of anti-tumor treatment, such as chemotherapy, immunotherapy, radiation treatment, and surgery, used to treat hard tumours (melanoma, lung disease, and colorectal cancer). So, in conclusion xenometabolites helps to boost the host immune system.

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Authors declare that they have no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate

Corresponding and all the co-authors are willing to participate in this manuscript.

Consent for Publication

All authors are willing for publication of this manuscript

Data Availability

Even though adequate data has been given in the form of tables and figures, however, all authors declare that if more data required then the data will be provided on request basis.

Author Contributions

FI, AI, MUA, proposed this idea and drafted initial manuscript. SB, IA, IU, IFUR, MAS, US, SA, helped in preparing figures and tables and overall quality of the manuscript.

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