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Review:**Drug pharmacomicrobiomics and toxicomicrobiomics: from scattered reports to systematic studies of drug-microbiome interactions**

Ramy K. Aziz^{1*}, Shaimaa M. Hegazy², Reem Yasser², Mariam R. Rizkallah³, Marwa T. ElRakaiby¹

¹Department of Microbiology and Immunology, Faculty of Pharmacy, Cairo University, Cairo, Egypt; ²Undergraduate program, Faculty of Pharmacy, Cairo University, Cairo, Egypt;

³Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Germany

*** Corresponding Author:** ramy.aziz@gmail.com. Department of Microbiology and Immunology, Faculty of Pharmacy, Cairo University, 11562 Cairo, Egypt.

Institutional E-mail: ramy.aziz@pharma.cu.edu.eg, Phone: +(20)1007158450

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KEYWORDS

bioinformatics; genomics; normal flora; metabolomics; metabonomics; microbiota; microbiome; systems biology; systems pharmacology; toxicology

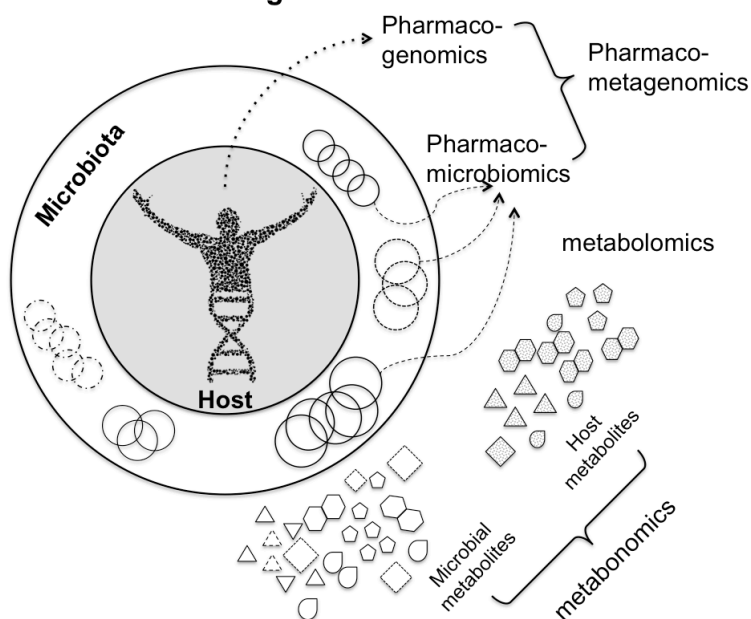
ABSTRACT

Introduction: Pharmacomicrobiomics and toxicomicrobiomics study how variations within the human microbiome (the combination of human-associated microbial communities and their genomes) affect drug disposition, action, and toxicity. These emerging fields, interconnecting microbiology, bioinformatics, systems pharmacology, and toxicology, complement pharmacogenomics and toxicogenomics, expanding the scope of precision medicine.

Areas covered: This article reviews some of the most recently reported pharmacomicrobiomic and toxicomicrobiomic interactions. Examples include the impact of the human gut microbiota on cardiovascular drugs, natural products, and chemotherapeutic agents, including immune checkpoint inhibitors. Although the gut microbiota has been the most extensively studied, some key drug-microbiome interactions involve vaginal, intratumoral, and environmental bacteria, and are briefly discussed here. Additionally, computational resources, moving the field from cataloguing to predicting interactions, are introduced.

Expert opinion: The rapid pace of discovery triggered by the Human Microbiome Project is moving pharmacomicrobiomic research from scattered observations to systematic studies focusing on screening microbiome variants against different drug classes. Better representation of all human populations will improve such studies by avoiding sampling bias, and the integration of multi-omic studies with designed experiments will allow establishing causation. In the near future, pharmacomicrobiomic testing is expected to be a key step in screening novel drugs and designing precision therapeutics.

Pharmacomicrobiomics and associated technologies



Relevant -omics approaches

- “Who is there?”
Identity/ Community structure
➤ 16S microbiome profiling
- “What are they able to do?”
Encoded proteins/ metabolic potential
➤ (Meta)Genomics
- “What are they about to do?”
Transcribed message
➤ (Meta)Transcriptomics
- “What are they doing?”
Proteins: the functional units
➤ (Meta)Proteomics
- “What have they actually done?”
Reaction products/ intermediates
➤ Metabolomics/Metabonomics

Different subfields associated with pharmacomicrobiomics and the multiple -omics technologies that can be used to study drug-microbiome interactions. The left panel depicts the human genome, at the center, surrounded by a microbial cloud (the microbiota), which affects xenobiotics through the produced metabolites. The right panel shows the different systems-levels approaches for understanding what is encoded by host-associated microbial genomes.

Article Highlights:

- Pharmacomicrobiomics describes the effect of microbiome variations on drug fate and action.
- Toxicomicrobiomics can be defined as the effect of microbiome variations on xenobiotics, poisons, and drug adverse effects.
- The human gut microbiota differentially affects the bioavailability and efficacy of dozens of drugs. Classical examples include digoxin metabolism and acetaminophen toxicity.
- Some more complex interactions involve an interplay between the gut microbiota, immune system, and administered drugs, such as the case of cyclophosphamide and immune checkpoint inhibitors.
- In addition to cardiovascular and anticancer drugs, plant xenobiotics and other dietary supplements are among the chemicals that are mostly affected by the gut microbiota, which has long adapted to these dietary components.
- Other than the gut microbiota, vaginal bacteria may inactivate the antiviral agent tenofovir, and intratumoral bacteria were shown to inactivate the anticancer agent, gemcitabine.
- In the future, better-designed, more inclusive microbiome-wide studies will improve the predictive value of microbiome types, and pharmacomicrobiomic testing is expected to improve precision therapeutics.

1. INTRODUCTION

The completion of the Human Genome Project at the start of this millennium [1, 2] provided a draft blueprint for the human species and ushered in a new era in biological sciences marked with big data, high throughput experiments, and systems-level approaches to understanding human phenotypes.

It was anticipated that sequencing those three billion letters that make up the genome of *Homo sapiens* would finally unravel the genetic basis of every disease and would account for most phenotypic differences among humans. Yet, the human genome sequence came with its own surprises [3], the most striking of which was that the number of human genes turned out to be smaller than previously expected, and that variations within and between those genes did not fully account for the wide range of phenotypic variations among humans [4].

Since then, additional variability-driving factors, such as epigenetic, regulatory, and microbial factors [5, 6, 7] were to be explored. In particular, the human microbiota, classically described as the normal flora, started being considered as a major player in intra- and inter-individual variations [5].

Having intrigued microbiologists for over 100 years [8, 9], the human microbiota is currently the center of attention of physicians and human biologists as well. Each human is colonized, on average, with 10^{14} microbial cells, mostly residing in the gastrointestinal tract [10, 11], but also in the oral/nasal cavities, vagina, and on the skin [4, 12]. These microbes not only

outnumber nucleated human cells ($\sim 10^{13}$ cells), but also carry more genes and encode a more versatile metabolic potential than their human host [13, 14].

Although the impact of the human microbiome on health and disease is being diligently studied as a part of the Human Microbiome Project (HMP) [15] and the MetaHIT project [16], information about the effect of human-associated microbes on the outcome of pharmacotherapy [4, 17, 18, 19] is scattered and has not been systematically studied until very recently. These systematic studies started in parallel with the introduction of novel, interdisciplinary fields, such as pharmacometabonomics [20, 21] and pharmacomicrobiomics [4, 22].

Pharmacomicrobiomics is the study of drug-microbiome interactions, or how microbiome variations affect a drug's fate (pharmacokinetics) and action (pharmacodynamics) by activation, potentiation, competition, or biodegradation [4, 22]. It emerged as a natural expansion of pharmacogenomics, but instead of emphasizing on the effect of human genome variations on pharmacotherapy, it deals with the human supraorganism [23, 24], underlining the role of human-associated microbiomes, with all their metabolic potential (Table 1).

Human microbiome variations also affect how humans assimilate and respond to environmental toxins and xenobiotics in food, drugs, plants, and other natural products [19, 25, 26]. Thus, insights from microbiome research are also expanding toxicogenomics, the study of how human genome variations affect xenobiotics, poisons, and drug adverse effects, into a novel branch of toxicology, which we propose as *toxicomicrobiomics*.

Here we briefly review the most prominent examples of pharmacomicrobiomic and toxicomicrobiomic interactions, and we **highlight those drug-related interactions and mechanisms discovered since 2014**. Of note, the last five years have witnessed an expansion of knowledge about microbiome interactions with multiple drug classes; however, a large body of knowledge about chemotherapeutic agents has been particularly generated. We also review currently available online resources that help documenting or predicting drug-microbiome interactions as well as other tools that attempt to predict functions or metabolites from microbiome composition data.

Finally, while the gut microbiota has been the most studied one, perhaps because of the higher numbers of its members, their higher diversity, and the most strongly established correlation with human health, we also present cases in which non-gut or environmental microbiotas play a pivotal role in modulating drug metabolism and therapeutic outcomes.

2. BACKGROUND AND HISTORY

2.1. A decade of human microbiome research

The HMP was launched a decade ago, and was planned to be performed in two phases: a descriptive/cataloguing phase (Phase I or HMP1) [15, 27], and an integrative phase (Phase II or iHMP) [28, 29]. In parallel, MetaHIT, a massive metagenomic study was conducted in the European Union, with a similar vision but with a more focused scope (the human gut) [16].

Microbiome studies of all sorts were conducted in parallel to the HMP and MetaHIT, which were indeed a trigger for a new era in microbiological research, reconciling an old, artificial dichotomy between environmental and medical microbiology [30]. This reconciliation coincided with the rise of the 'One Health' concept, an approach to addressing health problems by integrating human, animal, and environmental studies [31, 32].

The main HMP questions relevant to this review's topic are: **Are their certain core and signature microbiomes for different body sites? Are there particular clusters or "microbiome types" that can be used to stratify individuals for achieving precision medicine? What are the major factors that influence an individual's microbiome, thus influencing the so many microbially driven phenotypes?**

The question of a core microbiome emerged as early as the first studies of Phase I (HMP1) [33]. In a sequel of the project, dubbed HMP1-II, an expanded dataset from the HMP1 cohort was analyzed by whole metagenome sequencing primarily targeting six body sites, at different time points, in 265 individuals [29]. Great effort was made to define core sets of metabolic pathways that characterize each of the six body sites. Given the high diversity of taxa and their genes, core pathways were defined as those detected in $\geq 75\%$ of individuals. These pathways were further classified into core, multicore, and supercore pathways. Overall, 258 pathways were core to at least one body site, 176 were core to body sites from multiple body areas (thus called multicore), and 28 were core to all six targeted body sites, earning the 'supercore' attribute [29]. A general conclusion for this work, which supports the HMP first reports [34], is that the core microbiome can be better defined functionally rather than taxonomically, reflecting functional adaptation by the microbiota to specific body sites [29].

For example, nitrate reduction is a site-enriched pathway in the oral cavity, which suggests a functional adaptation of the oral microbes to a particular niche of the human body. A metagenomic analysis of the healthy oral microbiome identified 14 species that act as nitrate reducers, and provide the human body with continuous sources of nitrite and nitric oxide [35]. Colonization of the oral cavity by these denitrifying bacteria contributes to the host nitric oxide (NO) homeostasis.

Similarly, the degradation of complex plant carbohydrates is processed by two closely related gut Bacteroidetes [36]. Specifically, mannan, which is a plant-derived glycan found in human diet but not digested by human enzymes, is processed by polysaccharide-utilization loci in the dominant gut microbe, *Bacteroides thetaiotaomicron* [37]. The mannan degradation pathway is thus an example of a functionally adapted gut-specific pathway.

Based on the above notion of conservation of metabolic pathways even when taxonomic units vary, the initial distinction of the microbiome into different 'enterotypes' [38, 39] did not

seem to stand the test of time (see Table 1). First, as with any classification, critics suggested that there are no clear boundaries between different taxonomic types, and that the microbiome diversity would be better represented as a continuum of taxonomic variants. On the other hand, metabotypes [40, 41, 42], functional clusters that differentiate individuals based on their metabolome signatures, seem a better alternative for enterotypes, given that what bacteria do, rather than what species are there, is the main influencer on human health [8].

Regarding the question of key influencers on the microbiome structure or its metabolic potential, major changes in the gut microbiome were observed in response to environmental factors, especially diet [43]. The decreased Bacteroidetes-to-Firmicutes ratio in obese individuals was initially linked to metabolic pathways such as the hydrolysis of polysaccharides in the intestinal lumen, leading to higher fat and calorie extraction from food than in lean individuals [44, 45]. In HMP1-II, a Gaussian process model was developed to study the temporal variability of the microbiome at different body sites. In the gut, inter-individual variation of Bacteroidetes, and in particular the genus *Bacteroides*, was markedly exhibited while Firmicutes were dynamic over time within individuals [29]. Thus, the Bacteroidetes-to-Firmicutes ratio may not be a reliable indicator of an individual's gut microbiome health given its potential temporal fluctuation.

Another obvious key influencer is human genetics [46]. Microbiome resilience was observed since the early microbiome studies, suggesting the existence of some 'microbiome memory' that is certainly a function of the host's genotype. When genomic DNA from the blood of 298 individuals of the HMP cohort donors was sequenced [47], the genetic principal components showed the strongest effect on the taxonomic composition and functional potential in the gut and oral microbiomes, but not in the nares or vaginal communities. For example, Caucasians had higher abundance of *Lachnospiraceae* bacterium, *Roseburia intestinalis*, and *Subdoligranulum* in stool than other races or ethnicities [47]. While such genetic association may be due to differences in dietary habits, the ability to digest/metabolize certain nutrients is significantly dictated by host genetics [48]; hence, the created microenvironment specifically influences the microbial community flourishing within the gut.

Taken together, whether the major influence is environmental, diet-related, or genetic, all previous insights suggest that early studies that focused on North American or European donors overlooked the impact of variations in geography and environment. Factors such as immune status, detailed diet, and pharmaceutical history of the donors have to be recorded and investigated, and—above all—real diversification that reflects the global distribution of human populations should be pivotal to next decade's microbiome studies.

2.2. The birth and rise of pharmacomicrobiomics

Only after the booming interest in human microbiome variations has the study of drug-microbiome interactions become a systematic discipline and became the main subject of the novel, interdisciplinary fields of pharmacometabonomics [20, 21], pharmacometagenomics [49], and pharmacomicrobiomics [4, 22].

The term *pharmacomicrobiomics* was first suggested in 2010 [4] to describe “the effect of microbiome variations on drug disposition, action, and toxicity.”

The key in defining pharmacomicrobiomics is investigating drug-microbiome interactions, i.e., the effect of variations of the *microbiome* (rather than individual microbes) on pharmacokinetics and pharmacodynamics. Interactions between drugs and individual microbes, on the other hand, have been studied for quite a while, in the context of drug biotransformation and biodegradation.

Other terms that describe studying the impact of the human microbiota on drugs are pharmacometabolomics [41, 50] and pharmacometabonomics [20, 51]. Both pharmacometabolomics and pharmacometabonomics are concerned with the systems-level study of microbial metabolites, but the latter takes in consideration a combination of genomics and metabolomics, whence the “n” in metabonomics [52]. It is possible to consider metabonomics as a synonym for “meta-metabolomics” [53], or the metabolomics of metagenomes.

Pharmacometabolomics and *pharmacometabonomics* focus on analyzing host- and microbiome-generated metabolites, and studying their diagnostic and predictive impacts on the pharmacological properties of administered drugs. However, these two closely related fields are not just confined to microbiome variations, but look at the final products of host-microbiome interactions: the metabolites resulting from drug processing by the human body and its associated microbiota. Metabolome variations are a consequence of multiple factors, some of which are genetic, such as human and microbial genome variations [50, 54]. Additionally, the metabolome is highly sensitive to transient and permanent changes in the microbial composition, metabolic regulation, and to diet and other environmental factors [55].

Finally, the term pharmacometagenomic(s) has also been suggested [49] to study variations in human response to drugs. It integrates the analysis of microbial genomes (or human-associated metagenomes) with the human genome itself, and can be seen as the metagenomics of the human holobiont. While metagenomics, by definition, is concerned with the types of species in an ecosystem (“who is there and how many?”) as well as the overall gene pool of the living form in that ecosystem (“what they are doing?”), the pharmacometagenomic approach emphasizes on shotgun analysis or random community genomics, and should thus be differentiated from amplicon (16S or 18S) analysis, which only primarily identifies the phylogenetic structure of living forms within an ecosystem.

What makes pharmacomicrobiomics stand out in comparison to these terms is that it combines microbial community composition (usually determined by 16S amplicon analysis—or 18S in the case of eukaryotic microbe) and functional potential (studied by metagenomics, metatranscriptomics, and metabonomics), all of which are simply parts of microbiomics. It is not always possible or easy to predict function from microbial community composition, and thus the combination of multi-omic technologies is always beneficial [55].

Table 1: A brief comparison between pharmacogenomics and pharmacomicrobiomics

Pharmacogenomics	Pharmacomicrobiomics
Dependent variables:	
Drug bioavailability and therapeutic outcome	
Independent variables:	
Inherited human genome variations or epigenetic variations	Variations in microbial composition, and microbial genome, transcriptome, and proteome
Intraindividual variations:	
An individual's genome is relatively stable (except for the rare mutations that may emerge during a lifetime). Pharmacogenetics and pharmacogenomics have largely dealt with the human organism as a one unit with homogenous cells and identical genomes; however, one possible application of intraindividual genetic variations is the study of variations between cancerous, somatic, and germline tissue [56].	Variations are dynamic and mobile. The microbiome is akin to a cloud [22] because the microbial composition is temporally, spatially, and hormonally variable within one individual. In addition to subtle and continuous variations caused by internal factors, dramatic variations may be caused by dietary changes and other environmental factors, such as humidity/dryness.
Interindividual variations:	
Most of the documented pharmacogenetic and pharmacogenomic variations describe allelic variations between different individuals. Among the most popular allelic variations are those in drug-metabolizing liver enzymes, notably the cytochromes. Additional drug action-modulating allelic variations may be in human leucocyte antigens (HLA), transporters, or drug target molecules/receptors. A typical example is the variability in warfarin treatment and toxicity outcome, which depends on many factors, one of which is the variation of its molecular target: Vitamin K epoxide Reductase Complex (VKORC) subunit 1.	Microbiome variations between individuals are still too complex to be fully catalogued and precisely classified. Initial studies, on the gut microbiome as an example, used several dimensionality-reduction methods to cluster different microbiome profiles. Initially, enterotypes were suggested [38, 39], which were marked by Bacteroidetes-to-Firmicutes or <i>Bacteroides</i> -to- <i>Prevotella</i> ratios. Later on, it was thought that enterotypes may be oversimplified, and that there is a gradient or continuum of types that can be described by some beta diversity metrics, such as UNIFRAC [57] or Bray-Curtis [58] diversity. Another way of seeing interindividual differences focuses on functional rather than microbial profile-based classifications, and thus describes functional clusters or metatypes. Simple biomarkers remain popular, notably the presence of some biomarker species such as <i>Fusobacterium</i> or <i>Prevotella</i> , as well as some probiotic species such as <i>Bifidobacterium</i> , or some biomarker genes, such as cardiac glycoside reductases, <i>cgr</i> [59].

3. ONLINE RESOURCES

Whereas plenty of well-established resources for pharmacogenetics and pharmacogenomics are available online (e.g., PharmGKB: <https://www.pharmgkb.org>, DrugBank: <https://www.drugbank.ca>, and Gene-Drugs: <https://cpicpgx.org/genes-drugs>, among others), online resources for drug-microbiome interactions are scarce.

An early attempt to systematically document non-antibiotic drug-microbe or drug-microbiome interactions was made in the PharmacoMicrobiomics database (<http://www.pharmacomicrobiomics.org>), released in 2011 [60] (See Box).

Additionally, *DrugBug* (<http://metagenomics.iiserb.ac.in/drugbug>), published in 2017 [61], uses machine learning to predict xenobiotic metabolism by gut microbial enzymes. The Microbial Drug Target Database, MDTD (URL: <http://chengroup.cumt.edu.cn/MDTD/>), is a recently developed database for microbial drug targets, and has more emphasis on antimicrobials or other microbiome-driven therapeutics.

In addition to these few tools directly addressing drug-microbiome associations, a hot research area of computational biology is emerging to address the gap in translating microbiome composition into potential functional implications (whether it is the coding potential of a microbiome based on known biology of its taxa [62] or metabolomics profile [63]). Among these, is a set of interestingly named tools for linking microbiome to function (e.g., MIMOSA [64], FISHTACO [65], and BURRITO [66]).

Box: The online PharmacoMicrobiomics portal

The PharmacoMicrobiomics database started as an educational initiative mostly curated by undergraduate students [67], and evolved into a web portal mining literature and linking PubMed abstracts to chemical and taxonomy databases [60].

Given the relatively small size of the database, it remains difficult to assess its usage and usefulness. Nevertheless, from visitor data recorded between January 2015 and February 2018, some indicators regarding the most viewed interactions and the most hoped-for interactions can be noted. The most viewed interactions are: environment-ibuprofen (97 out of 2585 views), gut-baicalin (95 views), gut-digoxin (84 views), gut-acetaminophen (71 views), gut-irinotecan (57 views), gut-omeprazole (56 views), gut-polyphenols (56 views), gut-cyclophosphamide (51 views).

The most searched drugs, compared to all unique searches, are: NSAIDs, aspirin, acetaminophen and ibuprofen (42 out of 835 searches, combined), digoxin (19/835), irinotecan (15 searches), cyclophosphamide (14 searches), and metformin (13 hits). Furthermore, the non-drug terms are: cancer (12 searches), skin (4 searches), and gut (4 searches).

Of those searched drugs and terms, only “aspirin” has no database matches. Moreover, interactions linked to cancer and chemotherapeutic agents seem to be the most queried interactions.

Table 2: Recently reported pharmacomicrobiomic and toxicomicrobiomic interactions

Drug (CID)	Microbiome (site or taxon)	Type of interaction	Year	Reference
L- tryptophan (6305)	Unknown gut microbes	Gut microbes convert L-tryptophan into the bioactive neurotransmitter tryptamine but generate a toxic byproduct.	2014	[68]
Geniposide (107848)	Unknown gut microbes	Gut microbes decrease Geniposide's bioavailability.	2014	[69]
Lovastatin (53232)	Unknown gut microbes	Gut microbes increase Lovastatin's activity.	2014	[70]
Metformin (4091)	Unknown gut microbes	Gut microbes enhance metformin antidiabetic activity	2014	[71]
Gemcitabine (60750)	<i>Mycoplasma hyorhinis</i>	<i>Mycoplasma hyorhinis</i> decrease gemcitabine's activity.	2015	[72]
Ellagic acid (5281855)	Unknown gut microbes	Gut microbes increase ellagic acid's activity.	2015	[73]
Berberine (160447)	Unknown gut microbes	Gut microbes increase berberine bioavailability by converting it into an absorbable form.	2015	[74]
Naringin (442428)	<i>Bifidobacterium dentium</i>	Intestinal microbes increase naringin metabolism.	2015	[75]
Poncirin (442456)	<i>Bifidobacterium dentium</i>	Intestinal microbes increase poncirin metabolism.	2015	[75]
Rutin (5280805)	<i>Bifidobacterium dentium</i>	Intestinal microbes increase rutin metabolism.	2015	[75]
PD-1 inhibitors	<i>Bifidobacterium</i>	Gut microbes enhance the activity of PD-1 inhibitors.	2015	[76]

Grape seed polyphenol extract, GSPE	Unknown gut microbes	The intestinal microbiota converts GSPE to active metabolite	2015	[77]
Amlodipine (2162)	Unknown gut microbes	Gut microbes metabolize the drug, altering its bioavailability	2016	[78, 79]
Tenofovir (464205)	<i>Gardnerella vaginalis</i> (Urogenital microbiome)	The vaginal microbe, <i>Gardnerella vaginalis</i> , increases tenofovir's metabolic processing.	2017	[80]
Fluoxetine (3386)	Environmental consortium	Microbial consortia increase fluoxetine's degradation.	2017	[81]
Mefenamic Acid (4044)	Environmental consortium	Microbial consortia increase mefenamic acid 's degradation.	2017	[81]
Metoprolol (4171)	Environmental consortium	Microbial consortia increase metoprolol's degradation.	2017	[81]
Oxaliplatin (71301229)	Unknown gut microbes	Gut microbes increase oxaliplatin's toxicity.	2017	[82]
Doxorubicin (31703)	<i>Raoultella planticola</i>	<i>Raoultella planticola</i> and other Enterobacteriaceae increase doxorubicin metabolism.	2018	[83]
Salicin (439503)	<i>Lactobacillus acidophilus</i>	Gut microbes (species: <i>Lactobacillus acidophilus</i>) increase salicin's activity.	2018	[84]
Nifedipine (4485)	Unknown gut microbes	Gut microbes metabolize metabolism, affecting its bioavailability and efficacy.	2018	[85]

4. AN UPDATE ON DRUG-MICROBIOME INTERACTIONS (Table 2)

Perhaps the best-studied examples of gut microbiome involvement in drug metabolism are the cases of acetaminophen and digoxin.

Acetaminophen, being analogous to a microbial secondary metabolite (*p*-cresol) has variable toxicity depending on the amounts of *p*-cresol produced by an individual's microbiota. In this case, *p*-cresol competes with detoxifying enzymes in the liver, which positively influences the painkiller's hepatotoxicity. This example has been quite well characterized with detailed metabonomic analyses of factors influencing the interaction and the extent of hepatotoxicity [51]. This microbiome-induced liver injury was further found to follow a diurnal cycle, mediated by the gut metabolite 1-phenyl-1,2-propanedione [86].

Digoxin, a typical cardiac glycoside well known in pharmacology and pharmacokinetics for its narrow therapeutic range, is a drug whose dose should be carefully adjusted. If its bioavailability slightly drops, the pharmacological effect is not reached, and if it slightly increases, adverse effects appear. The impact of microbiome variations on digoxin has been documented for decades [87], and it was one of the drugs whose metabolizing bacteria, *Eggerthella lenta* (formerly *Eubacterium lentum*), have been identified [59, 88]. However, only recently the actual mechanism by which the bacteria degrade digoxin was revealed, and the finding was intriguing because only a few strains of these bacteria were found to possess the cardiac glycoside reductase genes (*cgr*), which encode the degrading enzymes [59]. The distribution of these genes in human metagenomes, their polymorphism, and their enzymatic activity have just started to be determined in 2018 [89].

A third classical interaction is one involving both the bacteria and the immune system in an interesting synergism between the chemotherapeutic agent, cyclophosphamide, and microbiome-translocated immune cells. The triad: Th17 cells, gut Firmicutes, and cyclophosphamide conspire against cancer cells, providing a prototypic example of a positive loop that starts with a drug-induced alteration in microbiome structure, leading to immune translocation, which, in turn, potentiates the drug action [90].

After these pioneering studies were published, pharmacomicrobiomic testing appealed to many academic and industrial research laboratories, especially with drugs having narrow therapeutic range, high toxicity, or those that are too expensive to be empirically prescribed. It was suggested that pharmacomicrobiomic/ metagenomic testing be added to therapeutic regimens [91, 92].

Of note, in the past few years, several excellent reviews have been published to catch up with this rapidly emerging research area, with emphasis on different aspects of pharmacomicrobiomics (e.g., pharmacological [93], toxicological [94], microbiological, or chemical perspectives). Some published articles focused on certain classes of drugs (e.g., antihypertensive [95], immunotherapeutic [96], or chemotherapeutic agents [97]), and a recent methodological article summarized state-of-the-art laboratory procedures to study microbiome effects on drug disposition [98].

To avoid redundancy, the focus of this review article is on the most recent advances in pharmacomicrobiomics and toxicomicrobiomics, with emphasis on studies published in the past five years.

4.1. Pharmacomicrobiomics of cardiovascular drugs

Other than digoxin, cardiovascular drugs have been investigated for a microbiome factor. Several recent studies focused on the potential impact of gut microbes on heart diseases, the most recent of which investigated microbial metabolism of two antihypertensive medications, amlodipine and nifedipine. These calcium channel blockers are differentially metabolized by gut microbes to inactive metabolites, resulting in a decrease of their antihypertensive effect. The role of the microbiome in their metabolism was seldom considered but seems to influence their activity [78, 79, 95], and might be manipulated by induced hypoxia [85].

The second study tested a common nutrient, choline. The vitamin-like nutrient was found to be involved in atherogenicity through microbial gut metabolism. The gut microbiota metabolizes choline into trimethylamine (TMO), which is further metabolized in the host liver to trimethylamine-N-oxide. The final product of gut and liver metabolism can aggravate atherogenesis and coronary heart disease. This finding suggests that caution should be exercised when supplementing choline to high-risk individuals [99].

Within the same theme of microbiome influence on heart diseases, the effect of antibiotic administration on gut microbial metabolism of the lipid-lowering drug lovastatin was investigated. Gut microbes normally metabolize lovastatin to a number of metabolites, including the active hydroxy acid metabolite. Antibiotic administration was demonstrated to markedly decrease systemic concentration of the active metabolite, posing an alarming drug-drug interaction between lovastatin and broad-spectrum antibiotics [70].

4.2. Pharmacomicrobiomics of plant xenobiotics and dietary supplements

While drugs are the central focus of pharmacomicrobiomics, a large set of xenobiotics of natural origin, such as medicinal plant extracts and other dietary supplements, are also being studied for their interactions with the microbiome.

An accidental discovery unveiled a rare type of interaction, involving the nervous system. The enzyme tryptophan decarboxylase, responsible for converting tryptophan to the neurotransmitter tryptamine, was found in two gut microbes: *Clostridium sporogenes* and *Ruminococcus gnavus*. The discovery was made when an unexpected metabolite of tryptophan was found in the culture fluid of *C. sporogenes*. After further investigations, the rare enzyme was discovered in *C. sporogenes*, and the synthesized tryptamine was found to be secreted by the gut bacterium. Of note, the gene *trp decarboxylase* was incorrectly annotated as *tyr decarboxylase*, but the enzyme was tested in the presence of both amino acids, it decarboxylated tryptophan 600 times more efficiently than tyrosine, indicating that referring to the enzyme as tyrosine decarboxylase was inaccurate [68].

This interaction is not just important on the nutritional level, but it could also have implications with the use of tryptophan as a supplement or in multivitamin preparation. A fresh report has linked tryptophan metabolites to microglial control of astrocytes, suggesting a role for

the dietary amino acid in protection against some neurodegenerative diseases such as multiple sclerosis [100].

Although the majority of drug-microbiome interactions involve drug inactivation, some are crucial to increasing drug efficacy. A good example is the role of gut microbes in berberine absorption. Berberine is an alkaloid found in *Coptis chinensis*, a plant traditionally used for treating diarrhea and recently for treating metabolic syndrome. The mechanism of berberine absorption was poorly understood, as the drug has low water solubility. Gut microbes transform berberine into the water-soluble metabolite, dihydroberberine. Once absorbed, dihydroberberine is converted back to berberine and initiates its pharmacological effect [74].

Drug activation by the microbiota seems to be common in bioactive plants and their medicinal products. For example, grape seed polyphenol extract (GSPE), commonly known for its antioxidant activity, contains a number of polyphenolic compounds that were proven to possess neuroprotective activity and has been used for Alzheimer's disease ever since. A study investigated the impact of GSPE on mice with Alzheimer's disease, focusing on the active participation of intestinal microbiota in GSPE's activity. Gut microbes convert polyphenols to phenolic acids. Two particularly important ones (3-hydroxybenzoic acid and 3-(3'-hydroxyphenyl)propionic acid) were measured in the brain and showed an increase after GSPE administration. Those phenolic acids were responsible for delaying neurodegeneration by inhibiting β -amyloid aggregation in the brain and therefore stopping Alzheimer's disease progression [77].

Another good example of mutualism is provided by *Lactobacillus acidophilus* and the plant glycoside salicin. The intestinal bacteria use the sugar part of the glycoside to grow while leaving the active aglycone part to be readily absorbed by the host. Two key elements were identified for this process to be completed: Phosphotransferase system (PTS) transporters and phospho- β -glucosidases are responsible for glycoside uptake and hydrolysis. This interaction is beneficial for both the microbe and the host and it highlights the role of *Lactobacillus acidophilus* in increasing benefit from plant glycosides through metabolism [84, 101]. Rhamnoglucosidases are also involved in this interaction. The bacterium *Bifidobacterium dentium* possesses α -L-rhamnosidase enzyme enabling it to hydrolyze rutin, poncirin and naringin, but not quercitrin [75].

4.3. Pharmacomicrobiomics and toxicomicrobiomics of anticancer agents

One of the major and most dramatic impacts of human microbiome variations on drug therapy is that on chemotherapeutic agents. In addition to the archetypal example of cyclophosphamide (see above), a few other interactions were recently reported, opening a big area of research that may improve the outcome of chemotherapy and decrease its toxicity. For example, the human microbiota was found to activate ellagic acid, modulate the toxicity of irinotecan [102], and exert major impact on other chemotherapeutic agents, such as oxaliplatin and cisplatin [82], through interaction with the immune system.

Other than cyclophosphamide's synergy with the immune system, a good example of a cytotoxic drug potentiation is the activation of the natural product, ellagic acid. Urolithin A, a metabolite of ellagic acid generated by gut microbes, could increase the sensitivity of colorectal cancer (CRC) cells to 5-fluorouracil (5-FU: an anti-tumor anti-metabolite used for CRC). This

finding suggests that a combination of 5-fluorouracil and ellagic acid may lead to 5-FU dose reduction and decreased toxicity and, most importantly, increased benefit from the reduced dose [73].

Immune checkpoint inhibitors act through a distinct anticancer effect, by blocking pathways that suppress immunity. They inhibit tumor growth and promote regression by immune modulation. A prominent subset is PD-1 inhibitors, the drugs that block this T cell checkpoint molecule, which is otherwise used by tumors to drive the immune cell to its own death. However, a discrepancy among the effectiveness of these inhibitors was observed, as patient response remained as low as 25 % in some cases [103], which was hypothesized to be associated with the gut microbiome.

Combination treatment of *Bifidobacterium* and a PD-1 inhibitor nearly abolished tumor outgrowth and decreased relapse. This effect was thought to be driven by the augmentation of dendritic cell function and accumulation of CD8 T cells in the tumor microenvironment [76]. On the other hand, not all commensals showed a similar effect to the previous. Bacteroidales overrepresentation was accompanied by a poor response to immune checkpoint inhibitors.

Likewise, other studies demonstrated an added benefit of the overrepresentation of *Faecalibacterium*, Clostridiales and Ruminococcaceae in increasing the immune response to immune checkpoint inhibitors. Moreover, abundance of *Akkermansia muciniphila* showed greater response to these anticancer drugs [96]. Whether these promising findings, mostly based on mouse models, can be extrapolated to humans is controversial but may be possible in the near future [96].

One of the adverse effects of another immune checkpoint inhibitor, ipilimumab, was found to be microbe mediated. Patients with abundance of bacteria belonging to Phylum Bacteroidetes, including the families Bacteroidaceae and Rikenellaceae, were less susceptible to ipilimumab-induced colitis suggesting their possible protective role on the colon through polyamine transport and vitamin B biosynthesis [104].

Members of consortia within the gut microbiome may alter the response to anti-cancer medications most commonly by increasing their metabolism. This increase in metabolic processing may simply inactivate the drug, or may in addition increase its adverse effects (Table 3).

The growing list of microbial interactions with anticancer agents includes the antitumor antibiotic doxorubicin. When tested in the model organism, *Caenorhabditis elegans*, doxorubicin was inactivated through the removal of its sugar (deglycosylation). This deglycosylation, which generates 7-deoxydoxorubicinol and 7-deoxydoxorubicinolone, was catalyzed by a molybdopterin-dependent enzyme found in *Raoultella planticola* and other members of family Enterobacteriaceae [83].

Geniposide, an iridoid glycoside found in *Gardenia* extract exhibits anti-tumor and anti-inflammatory effects. It was specifically involved in reducing the injurious effect of formaldehyde on neuroblastoma cells by inhibiting apoptosis through Bcl-2 proteins expression [105]. Geniposide is metabolized by microbial beta-glucosidases to Genipin [69], which can contradict the effect to Geniposide by inducing cytotoxicity through the JNK pro-apoptotic pathway in

HepG2 cells [106]. These findings provide a striking example of the role of intestinal microbial metabolism in not only altering drug efficacy through metabolic processing, but also in modulating its toxicity: a combination of pharmacomicrobiomics and toxicomicrobiomics.

Oxaliplatin, a chemotherapeutic agent known for causing chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients, may not be the culprit for that adverse condition, after all, and provides another excellent example of toxicomicrobiomic interactions. A recent study investigated the influence of gut microbes on CIPN by testing two groups of mice: a gut microbe-free group and a gut microbe-harboring group. The findings supported the suggestion that gut microbes were majorly involved in CIPN pathogenesis by initiating an inflammatory response to oxaliplatin in dorsal root ganglion. A more detailed insight into the mechanism involves macrophage stimulation by bacterial lipopolysaccharide (LPS) and release of IL-6 and TNF α and consequently developing mechanical hyperalgesia. The microbe-free mice, on the other hand, did not develop mechanical hyperalgesia. However, after introducing exogenous LPS, CIPN was observed in this group providing further evidence that gut microbes-driven LPS plays a direct role in the induction of peripheral neuropathy [82].

An intriguing toxicomicrobiomic interaction was identified for irinotecan. What makes this interaction surprising is that it can be either beneficial or detrimental under different conditions. It was previously discovered that gut microbes can increase irinotecan toxicity owing to their possession of β -glucuronidase enzyme that removes glucuronide conjugation from irinotecan's toxic metabolite: SN-38G, and causes its enterohepatic circulation. This effect was inhibited by ciprofloxacin administration [107].

The glucuronidase-mediated toxicity was described in a study as being inhibitable by different means; yet, this inhibition is quite specific, and different enzyme orthologs do not respond similarly to different inhibitors, owing to structural changes [108]. A potent glucuronidase inhibitor, amoxapine, could decrease this toxicity when co-administered with irinotecan [109]. On another front, a beneficial microbial effect was associated with increasing the intake of prebiotic dietary fibers, which reversed the irinotecan-associated toxicity by increasing intestinal butyrate concentration [102].

Table 3: A simple classification of pharmacomicrobiomic and toxicomicrobiomic drug interactions, with representative examples.

Drug activity	Drug toxicity	Gut	Non-Gut
Drug activation	–	Berberine Ellagic acid Lovastatin Salicin Grape Seed Polyphenol Extract (GPSE)	
Enhancement of activity		PD-1 inhibitors Metformin Cyclophosphamide	
Drug inactivation	–	Digoxin Doxorubicin Rutin Poniricin Naringin Amlodipine Nifedipine	Tenofovir Fluoxetine Metoprolol Mefenamic acid Gemcitabine
Drug reactivation	Increased toxicity	Irinotecan L-Tryptophan	
Drug inactivation	Increased toxicity	Acetaminophen Geniposide Choline	Azo dyes*
–	Increased toxicity	Oxaliplatin	
–	Decreased toxicity	ipilimumab	

* Bacterial azoreductases are able to reduce azo dyes, present in some topical products; however, some of the degradation products may be carcinogenic.

4.4. Pharmacomicrobiomics outside the gut

One of the most remarkable recent discoveries, published in 2017 [80], is about the role of the vaginal microbe *Gardnerella vaginalis* in metabolizing the anti-HIV drug, tenofovir. This example is particularly interesting because the bacterial species involved was identified. In addition, it drew attention because the bacteria are differentially represented among women. African women tested in this study were classified according to their vaginal microbial colonization into those with a *Lactobacillus*-dominant microbiota and those with a non-*Lactobacillus*-dominant microbiota. The *Lactobacillus*-dominant group responded three times more to tenofovir than the non-*Lactobacillus* group. This major difference was explained by the

predominance of *Gardnerella vaginalis* in the *Lactobacillus*-deficient group, which leads to bacterial vaginosis. In conclusion, *G. vaginalis* was deemed responsible for decreasing tenofovir's bioavailability by increasing its metabolism [80].

Another striking extra-intestinal example is the inactivation of gemcitabine (2',2'-difluorodeoxycytidine) by intratumor bacteria in pancreatic ductal adenocarcinoma (PDAC) [110]. The enzyme cytidine deaminase was found responsible for decreasing the efficacy of the anticancer agent by catalyzing the conversion to the inactive metabolite 2',2'-difluorodeoxyuridine, this phenomenon was also observed in colon cancer models by Gammaproteobacteria [111].

Mycoplasma hyorhinis cytidine deaminase was identified to have a similar effect on gemcitabine in breast cancer cell cultures. In this case, gemcitabine deactivation was reversed by the addition of a cytidine deaminase inhibitor, namely, tetrahydrouridine [72].

4.5. Environmental pharmacomicrobiomics and toxicomicrobiomics

The scope of drug-microbiome interactions may be expanded beyond the human microbiome to environmental microbiology and biodegradation. Drugs that are regularly consumed can reach the sewage as whole drugs or metabolites, and are potentially toxic to aquatic organisms. However, some naturally occurring nitrifying bacteria may reduce the harmful effect of pharmaceuticals. Metoprolol, fluoxetine and mefenamic acid were studied in the presence of ammonium nitrite-oxidizing bacteria, nitrite-oxidizing bacteria, and heterotrophic biomass. Biodegradation of the three drugs was highest with the ammonium nitrite-oxidizing bacteria, metoprolol had the least sorption on biomass and therefore the least biodegradation. This observation is a good example for the effect of a drug's physicochemical properties on its biodegradation [81].

Plenty of other examples of drug biodegradation in the environment may be soon the target of systematic studies to accelerate the discovery of human microbiome-induced drug inactivation, potentiation, or modification. It will always be safer and easier to study the interactions in the environment before trying to find similar ones by closely related bacteria residing in the human body.

5. CONCLUSION

In conclusion, pharmacomicrobiomics, pharmacometabonomics, pharmacometagenomics, and toxicomicrobiomics are all research areas that emerged briefly after the HMP was launched. These nascent research areas may lead to a paradigm shift in targeted therapeutics and precision medicine, especially with drugs of narrow therapeutic index, highly variable therapeutic outcome, or high cost. Microbiome studies are undoubtedly becoming an essential component of precision medicine and systems pharmacology, and in the near future pharmacomicrobiomic testing will become part of the clinical decision making for many drugs.

6. EXPERT OPINION: Outlook—the future of pharmacomicrobiomics and toxicomicrobiomics

6.1 From scattered reports on drug-microbe interactions to systematic studies of drug-microbiome interactions

From what was presented in this review article, it is fair to say that pharmacomicrobiomics is not a completely novel field or approach. The effect of the intestine and its microbiota on drug disposition is well documented in pharmacokinetics and bioavailability literature. Additionally, for over a century, individual drug-microbe interactions have been described and investigated through very clever experiments.

However, what is new and worth nurturing is taking studies of drug-microbe interactions to a systems level through integrating multiple -omics approaches [e.g., 51, 59, 112, 113]. The transition to this systems-level approach has been well synchronized with technological advances in DNA sequencing, robotics, mass spectrometry, proteomics, and metabolomics. The exciting rise of microbiome studies, pharmacomicrobiomics, pharmacometabonomics, and metagenomics of the human holobiont coincides with the massive expansion of computational biology, and the ability to handle big data using data mining and machine learning methods.

Another remarkable difference that can be observed in drug-microbiome studies conducted in the last few years is the move towards systematic prospective or case-control studies, and we expect systematic pharmacomicrobiomic screens to be implemented in drug-development pipelines in the coming decade. Most of the earlier reports were coincidental or scattered observations that were subsequently analyzed in depth. The latest studies, on the other hand, seem to be more organized and systematic. It is not unlikely to see massive screening of particular drugs against libraries of human-associated bacterial species, or massive screening of some well-characterized human bacteria against libraries of drugs and chemicals. In our opinion, such systematic high-throughput screening will uncover tens of additional drug-microbiome interactions that have not been previously considered. In addition, as the HMP evolves and as thousands of amplicon-based or shotgun metagenomic data sets are being made publicly available, virtual screening for drug-metabolizing enzymes, pathways, microbes, or microbial consortia will also be handy.

A clear gap in the field is the lack of robust computational tools of predictive value that are focused on drug-microbe interactions, whereas a good number of tools is being developed for predicting functional potential, metabolites, and microbe-microbe interaction networks. The current resources are scarce and are focused on cataloguing known interactions rather than predicting new ones. A novel prediction tool was developed [61], but remains preliminary, with an ability to predict enzyme families /microbial taxa with broad specificity. It seeks predicting enzymatic activities (digitized as EC numbers) that are well defined in members of the human microbiota; however, its accuracy remains to be improved.

In general, predictive tools need to advance on two fronts: (i) predicting interactions based on chemical analogy to existing drugs/xenobiotics, and (ii) predicting interactions based on metabolic potential and enzymatic activities within members of the microbiota (regardless of the taxonomic identity of these members), and these can build on the current tools for functional and metabolomics prediction (reviewed under “Online Resources”).

6.2. Some precautions, pitfalls, and areas for improvement

Like with all microbiome studies, in general, there are caveats to watch for when conducting pharmacomicrobiomic studies. One major precaution is not to confuse association and causation [54, 92]. Population-based studies or studies conducted on animal models often generate statistically robust correlations between a certain drug-microbiome pair and a phenotype; however, causation takes time to establish and, as seen with the example of cyclophosphamide [90], drug-microbiome interactions are often confounded by other factors such as the immune system, microbial translocation, and possibly interaction with diet and other drugs.

Another pivotal precaution is avoiding sampling bias. Strong economy, funding, and availability of well-established institutions are all factors that favor some countries (e.g., USA, Western Europe, China, and Japan). This increased share of research conducted in these countries inescapably leads to oversampling populations and ethnic groups living therein. As seen with many initial HMP and MetaHIT data, some conclusions and associations are only valid for some human populations, and the genetic effect may be behind many of the observed changes attributed to other phenotypes. Thus, sampling diverse patients is crucial in any future pharmacomicrobiomic studies to avoid the initial shortcomings of the HMP. Numbers of samples and sampling points are also important to provide statistical strength, and this too—unfortunately—strongly relies on economic factors, which places many countries and laboratories at a disadvantage, and compromises a fair and global representation of all humans.

One final hurdle to overcome is the difficulty to culture most of the microbiome members, in spite of recent breakthroughs [114, 115]. Many of the drug-microbiome interactions will require final experimental confirmation, at a level that is not possible without the ability to culture drug-modulating bacteria. However, some alternative technologies may be implemented, such as functional screening of metagenomic libraries against key drugs, or *in silico* screening for potential drug-modulating enzymes followed by their cloning and expression in heterologous hosts.

Lastly, the strong focus on chemotherapeutic agents is understandable and commendable, given the importance of precision therapy with these particular drugs, since they are life saving, mostly expensive, and with highly variable outcomes. However, expanding the scope towards all drug classes is necessary and imminent, and—in our opinion—will improve the knowledge about all drugs, inasmuch as specific chemical groups and bonds that are vulnerable to microbial enzymes will be delineated and classified.

6.3. The future?

Based on all the above, it is clear that pharmacomicrobiomics is rising, and more systematic screening is expected to enrich the field. Another similar aspect, toxicomicrobiomics, or the study of microbiome modulation of environmental pollutants, xenobiotics from natural products, and other food-associated toxins, is expanding as well.

These new trends, supported by latest technological advances, strengthen the current trend towards precision medicine and the One Health approach. Microbiome typing and pharmacomicrobiomic testing are expected to be added to treatment protocols and to drug

labels. The speed of such paradigm shift may be hard to predict, but its direction is clearly heading towards precision and predictive medicine [116], which is now experimentally, ethically, and economically favored.

REFERENCES:

1. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001 Feb 15;409(6822):860-921. doi: 10.1038/35057062 [doi]. PubMed PMID: 11237011; eng.
2. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science*. 2001 Feb 16;291(5507):1304-51. doi: 10.1126/science.1058040 [doi]. PubMed PMID: 11181995; eng.
3. Nelson NJ. Draft human genome sequence yields several surprises. *J Natl Cancer Inst*. 2001 Apr 4;93(7):493. PubMed PMID: 11287437; eng.
4. Rizkallah MR, Saad R, Aziz RK. The Human Microbiome Project, personalized medicine and the birth of pharmacomicrobiomics. *Curr Pharmacogenomics Person Med*. 2010;8(3):182-193. * First mention of the term "pharmacomicrobiomics"
5. Relman DA, Falkow S. The meaning and impact of the human genome sequence for microbiology. *Trends Microbiol*. 2001 May;9(5):206-8. doi: S0966-842X(01)02041-8 [pii]. PubMed PMID: 11336835; eng.
6. Richards CL, Bossdorf O, Verhoeven KJ. Understanding natural epigenetic variation. *New Phytol*. 2010 Aug;187(3):562-4. doi: 10.1111/j.1469-8137.2010.03369.x. PubMed PMID: 20659249; eng.
7. Maher B. ENCODE: The human encyclopaedia. *Nature*. 2012 Sep 6;489(7414):46-8. PubMed PMID: 22962707; eng.
8. Kendall AI. Some observations on the study of the intestinal bacteria. *J Biol Chem*. 1909 Nov 1;6:499-507. * A 1909 article discussing the important roles of the intestinal microbiota and likening the gut to a huge fermenter
9. Aziz RK. A hundred-year-old insight into the gut microbiome! *Gut Pathog*. 2009;1(1):21. doi: 10.1186/1757-4749-1-21 [doi]. PubMed PMID: 19968883; PubMed Central PMCID: PMC2797815. eng.
10. Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut microbiome. *Science*. 2006 Jun 2;312(5778):1355-9. PubMed PMID: 16741115.
11. Savage DC. Microbial ecology of the gastrointestinal tract. *Annu Rev Microbiol*. 1977;31:107-33. doi: 10.1146/annurev.mi.31.100177.000543 [doi]. PubMed PMID: 334036; eng.
12. Pflughoeft KJ, Versalovic J. Human microbiome in health and disease. *Annu Rev Pathol*. 2012;7:99-122. doi: 10.1146/annurev-pathol-011811-132421. PubMed PMID: 21910623; eng.
13. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006 Feb 24;124(4):837-48. doi: 10.1016/j.cell.2006.02.017 [doi]. PubMed PMID: 16497592; eng.
14. Cheesman SE, Guillemin K. We know you are in there: conversing with the indigenous gut microbiota. *Res Microbiol*. 2007 Jan-Feb;158(1):2-9. doi: 10.1016/j.resmic.2006.10.005 [doi]. PubMed PMID: 17223317; eng.
15. Turnbaugh PJ, Ley RE, Hamady M, et al. The Human Microbiome Project. *Nature*. 2007 Oct 18;449(7164):804-10. PubMed PMID: 17943116.
16. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010 Mar 4;464(7285):59-65. doi: 10.1038/nature08821 [doi]. PubMed PMID: 20203603; eng.
17. Sousa T, Paterson R, Moore V, et al. The gastrointestinal microbiota as a site for the biotransformation of drugs. *Int J Pharm*. 2008 Nov 3;363(1-2):1-25. doi: 10.1016/j.ijpharm.2008.07.009 [doi]. PubMed PMID: 18682282; eng. ** One of the most comprehensive reviews focusing on the chemical transformations of drug by gut bacteria
18. Wilson ID, Nicholson JK. The role of gut microbiota in drug response. *Curr Pharm Des*. 2009;15(13):1519-23. PubMed PMID: 19442168; eng.

19. Haiser HJ, Turnbaugh PJ. Developing a metagenomic view of xenobiotic metabolism. *Pharmacol Res.* 2013 Mar;69(1):21-31. doi: 10.1016/j.phrs.2012.07.009. PubMed PMID: 22902524; PubMed Central PMCID: PMC3526672. eng.
20. Clayton TA, Lindon JC, Cloarec O, et al. Pharmaco-metabonomic phenotyping and personalized drug treatment. *Nature.* 2006 Apr 20;440(7087):1073-7. doi: 10.1038/nature04648 [doi]. PubMed PMID: 16625200; eng.
21. Nicholson JK, Wilson ID, Lindon JC. Pharmacometabonomics as an effector for personalized medicine. *Pharmacogenomics.* 2011 Jan;12(1):103-11. doi: 10.2217/pgs.10.157 [doi]. PubMed PMID: 21174625; eng.
22. ElRakaiby M, Dutilh BE, Rizkallah MR, et al. Pharmacomicrobiomics: the impact of human microbiome variations on systems pharmacology and personalized therapeutics. *OMICS.* 2014 Jul;18(7):402-14. doi: 10.1089/omi.2014.0018. PubMed PMID: 24785449; PubMed Central PMCID: PMC4086029. eng.
23. Sleator RD. The human superorganism - of microbes and men. *Med Hypotheses.* 2010 Feb;74(2):214-5. doi: 10.1016/j.mehy.2009.08.047 [doi]. PubMed PMID: 19836146; eng.
24. Aziz RK. Rethinking pharmacogenomics in an ecosystem: drug-microbiome interactions, pharmacomicrobiomics, and personalized medicine for the human supraorganism. *Curr Pharmacogenomics Person Med.* 2012;10(4):258-261.
25. Johnson CH, Patterson AD, Idle JR, et al. Xenobiotic metabolomics: major impact on the metabolome. *Annu Rev Pharmacol Toxicol.* 2012 Feb 10;52:37-56. doi: 10.1146/annurev-pharmtox-010611-134748 [doi]. PubMed PMID: 21819238; eng.
26. Tralau T, Sowada J, Luch A. Insights on the human microbiome and its xenobiotic metabolism: what is known about its effects on human physiology? *Expert Opin Drug Metab Toxicol.* 2015 Mar;11(3):411-25. doi: 10.1517/17425255.2015.990437. PubMed PMID: 25476418; eng.
27. Peterson J, Garges S, Giovanni M, et al. The NIH Human Microbiome Project. *Genome Res.* 2009 Dec;19(12):2317-23. doi: 10.1101/gr.096651.109 [doi]. PubMed PMID: 19819907; PubMed Central PMCID: PMC2792171. eng.
28. Integrative HMP (iHMP) Research Network Consortium. The Integrative Human Microbiome Project: dynamic analysis of microbiome-host omics profiles during periods of human health and disease. *Cell Host Microbe.* 2014 Sep 10;16(3):276-89. doi: 10.1016/j.chom.2014.08.014. PubMed PMID: 25211071; PubMed Central PMCID: PMC5109542. eng.
29. Lloyd-Price J, Mahurkar A, Rahnavard G, et al. Strains, functions and dynamics in the expanded Human Microbiome Project. *Nature.* 2017 Oct 5;550(7674):61-66. doi: 10.1038/nature23889. PubMed PMID: 28953883; PubMed Central PMCID: PMC5831082. eng.
30. Ley RE, Knight R, Gordon JI. The human microbiome: eliminating the biomedical/environmental dichotomy in microbial ecology. *Environ Microbiol.* 2007 Jan;9(1):3-4. PubMed PMID: 17227400. * This article offers an important perspective on the convergence of environmental and (bio)medical microbiology.
31. Nolen RS. Mahr calls for 'one health' initiative. *J Am Vet Med Assoc.* 2006 Sep 1;229(5):640. PubMed PMID: 16972371; eng.
32. Evans BR, Leighton FA. A history of One Health. *Rev Sci Tech.* 2014 Aug;33(2):413-20. PubMed PMID: 25707172; eng.
33. Huse SM, Ye Y, Zhou Y, et al. A core human microbiome as viewed through 16S rRNA sequence clusters. *PLoS ONE.* 2012;7(6):e34242. doi: PONE-D-12-04736 [pii]. PubMed PMID: 22719824; PubMed Central PMCID: PMC3374614. eng.
34. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012 Jun 14;486(7402):207-14. doi: 10.1038/nature11234 [doi]. PubMed PMID: 22699609; eng.
35. Hyde ER, Andrade F, Vaksman Z, et al. Metagenomic analysis of nitrate-reducing bacteria in the oral cavity: implications for nitric oxide homeostasis. *PLoS ONE.* 2014;9(3):e88645. doi: 10.1371/journal.pone.0088645. PubMed PMID: 24670812; PubMed Central PMCID: PMC3966736. eng.
36. Martens EC, Lowe EC, Chiang H, et al. Recognition and degradation of plant cell wall polysaccharides by two human gut symbionts. *PLoS Biol.* 2011 Dec;9(12):e1001221. doi: 10.1371/journal.pbio.1001221. PubMed PMID: 22205877; PubMed Central PMCID: PMC3243724. eng.

37. Cuskin F, Lowe EC, Temple MJ, et al. Human gut Bacteroidetes can utilize yeast mannan through a selfish mechanism. *Nature*. 2015 Jan 8;517(7533):165-169. doi: 10.1038/nature13995. PubMed PMID: 25567280; PubMed Central PMCID: PMC4978465. eng.
38. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. *Nature*. 2011 May 12;473(7346):174-80. doi: 10.1038/nature09944. PubMed PMID: 21508958; PubMed Central PMCID: PMC3728647.
* A proposal and description of the so-called microbiome enterotypes
39. Siezen RJ, Kleerebezem M. The human gut microbiome: are we our enterotypes? *Microb Biotechnol*. 2011 Sep;4(5):550-3. doi: 10.1111/j.1751-7915.2011.00290.x. PubMed PMID: 21848611; eng.
40. Li M, Wang B, Zhang M, et al. Symbiotic gut microbes modulate human metabolic phenotypes. *Proc Natl Acad Sci USA*. 2008 Feb 12;105(6):2117-22. doi: 10.1073/pnas.0712038105 [doi]. PubMed PMID: 18252821; PubMed Central PMCID: PMC2538887. eng.
41. Kaddurah-Daouk R, Weinshilboum RM. Pharmacometabolomics: implications for clinical pharmacology and systems pharmacology. *Clin Pharmacol Ther*. 2014 Feb;95(2):154-67. doi: 10.1038/clpt.2013.217. PubMed PMID: 24193171; eng.
42. Guthrie L, Gupta S, Daily J, et al. Human microbiome signatures of differential colorectal cancer drug metabolism. *NPJ Biofilms Microbiomes*. 2017;3:27. doi: 10.1038/s41522-017-0034-1. PubMed PMID: 29104759; PubMed Central PMCID: PMC5665930. eng.
43. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014 Jan 23;505(7484):559-63. doi: 10.1038/nature12820. PubMed PMID: 24336217; PubMed Central PMCID: PMC3957428. eng.
44. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006 Dec 21;444(7122):1027-31. doi: 10.1038/nature05414 [doi]. PubMed PMID: 17183312; eng.
* A classic early microbiome paper that provides evidence for the role of the human microbiome in fat assimilation and subsequent obesity
45. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA*. 2004 Nov 2;101(44):15718-23. doi: 10.1073/pnas.0407076101 [doi]. PubMed PMID: 15505215; PubMed Central PMCID: PMC524219. eng.
46. Luca F, Kupfer SS, Knights D, et al. Functional genomics of host-microbiome interactions in humans. *Trends Genet*. 2018 Jan;34(1):30-40. doi: 10.1016/j.tig.2017.10.001. PubMed PMID: 29107345; PubMed Central PMCID: PMC5774629. eng.
47. Kolde R, Franzosa EA, Rahnavard G, et al. Host genetic variation and its microbiome interactions within the Human Microbiome Project. *Genome Med*. 2018 Jan 29;10(1):6. doi: 10.1186/s13073-018-0515-8. PubMed PMID: 29378630; PubMed Central PMCID: PMC5789541. eng.
48. Comerford KB, Pasi G. Gene-dairy food interactions and health outcomes: A review of nutrigenetic studies. *Nutrients*. 2017 Jul 6;9(7). doi: 10.3390/nu9070710. PubMed PMID: 28684688; PubMed Central PMCID: PMC5537825. eng.
49. Nayak RR, Turnbaugh PJ. Mirror, mirror on the wall: which microbiomes will help heal them all? *BMC Med*. 2016 May 4;14:72. doi: 10.1186/s12916-016-0622-6. PubMed PMID: 27146150; PubMed Central PMCID: PMC4857263. eng.
50. Kaddurah-Daouk R, Kristal BS, Weinshilboum RM. Metabolomics: a global biochemical approach to drug response and disease. *Annu Rev Pharmacol Toxicol*. 2008;48:653-83. doi: 10.1146/annurev.pharmtox.48.113006.094715 [doi]. PubMed PMID: 18184107; eng.
51. Clayton TA, Baker D, Lindon JC, et al. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. *Proc Natl Acad Sci USA*. 2009 Aug 25;106(34):14728-33. doi: 10.1073/pnas.0904489106 [doi]. PubMed PMID: 19667173; PubMed Central PMCID: PMC2731842. eng.
** A proposed mechanism for the effect of gut microbes on acetaminophen toxicity
52. Nicholson JK, Wilson ID. Opinion: understanding 'global' systems biology: metabonomics and the continuum of metabolism. *Nat Rev Drug Discov*. 2003 Aug;2(8):668-76. doi: 10.1038/nrd1157. PubMed PMID: 12904817; eng.

53. Ibrahim M, Anishetty S. A meta-metabolome network of carbohydrate metabolism: interactions between gut microbiota and host. *Biochem Biophys Res Commun*. 2012 Nov 16;428(2):278-84. doi: 10.1016/j.bbrc.2012.10.045. PubMed PMID: 23085046; eng.
54. Rosato A, Tenori L, Cascante M, et al. From correlation to causation: analysis of metabolomics data using systems biology approaches. *Metabolomics*. 2018;14(4):37. doi: 10.1007/s11306-018-1335-y. PubMed PMID: 29503602; PubMed Central PMCID: PMC5829120. eng.
55. Walker AW. Studying the Human Microbiota. In: Schwirtz A, editor. *Microbiota of the Human Body*. Advances in Experimental Medicine and Biology. Vol. 902. 2016/05/11 ed. Cham, Switzerland: Springer; 2016. p. 5-32.
56. McWhinney SR, McLeod HL. Using germline genotype in cancer pharmacogenetic studies. *Pharmacogenomics*. 2009 Mar;10(3):489-93. doi: 10.2217/14622416.10.3.489. PubMed PMID: 19650256; PubMed Central PMCID: PMC2722037. eng.
57. Lozupone C, Knight R. UniFrac: a new phylogenetic method for comparing microbial communities. *Appl Environ Microbiol*. 2005 Dec;71(12):8228-35. doi: 10.1128/aem.71.12.8228-8235.2005. PubMed PMID: 16332807; PubMed Central PMCID: PMC1317376. eng.
58. Mumby PJ. Beta and habitat diversity in marine systems: a new approach to measurement, scaling and interpretation. *Oecologia*. 2001 Jul;128(2):274-280. doi: 10.1007/s004420100643. PubMed PMID: 28547476; eng.
59. Haiser HJ, Gootenberg DB, Chatman K, et al. Predicting and manipulating cardiac drug inactivation by the human gut bacterium *Eggerthella lenta*. *Science*. 2013 Jul 19;341(6143):295-8. doi: 10.1126/science.1235872. PubMed PMID: 23869020; PubMed Central PMCID: PMC3736355. eng.
** One of the most complete papers determining both the bacterial species and genes responsible for digoxin inactivation
60. Rizkallah MR, S. G-E, Saad R, et al. The PharmacoMicrobiomics Portal: A database for drug-microbiome interactions. *Curr Pharmacogenomics Person Med*. 2012 Sep 1, 2012;10(3):195-203.
61. Sharma AK, Jaiswal SK, Chaudhary N, et al. A novel approach for the prediction of species-specific biotransformation of xenobiotic/drug molecules by the human gut microbiota. *Sci Rep*. 2017 Aug 29;7(1):9751. doi: 10.1038/s41598-017-10203-6. PubMed PMID: 28852076; PubMed Central PMCID: PMC5575299. eng.
62. Langille MG, Zaneveld J, Caporaso JG, et al. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. *Nat Biotechnol*. 2013 Sep;31(9):814-21. doi: 10.1038/nbt.2676. PubMed PMID: 23975157; PubMed Central PMCID: PMC3819121. eng.
63. Eng A, Borenstein E. An algorithm for designing minimal microbial communities with desired metabolic capacities. *Bioinformatics*. 2016 Jul 1;32(13):2008-16. doi: 10.1093/bioinformatics/btw107. PubMed PMID: 27153571; PubMed Central PMCID: PMC4920118. eng.
64. Noecker C, Eng A, Srinivasan S, et al. Metabolic model-based integration of microbiome taxonomic and metabolomic profiles elucidates mechanistic links between ecological and metabolic variation. *mSystems*. 2016 Jan-Feb;1(1). doi: 10.1128/mSystems.00013-15. PubMed PMID: 27239563; PubMed Central PMCID: PMC4883586. eng.
65. Manor O, Borenstein E. Systematic characterization and analysis of the taxonomic drivers of functional shifts in the human microbiome. *Cell Host Microbe*. 2017 Feb 8;21(2):254-267. doi: 10.1016/j.chom.2016.12.014. PubMed PMID: 28111203; PubMed Central PMCID: PMC5316541. eng.
66. McNally CP, Eng A, Noecker C, et al. BURRITO: an interactive multi-omic tool for visualizing tax-function relationships in microbiome data. *Front Microbiol*. 2018;9:365. doi: 10.3389/fmicb.2018.00365. PubMed PMID: 29545787; PubMed Central PMCID: PMC5837987. eng.
67. Aziz RK, Saad R, Rizkallah MR. PharmacoMicrobiomics or how bugs modulate drugs: an educational initiative to explore the effects of human microbiome on drugs. *BMC Bioinformatics*. 2011;12(Suppl 7):A10.
68. Williams BB, Van Benschoten AH, Cimermanic P, et al. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. *Cell Host Microbe*. 2014 Oct 8;16(4):495-503. doi: 10.1016/j.chom.2014.09.001. PubMed PMID: 25263219; PubMed Central PMCID: PMC4260654. eng.

69. Jin MJ, Kim IS, Kim DH, et al. Effects of intestinal microbiota on the bioavailability of geniposide in rats. *J Agric Food Chem*. 2014 Oct 8;62(40):9632-6. doi: 10.1021/jf502557f. PubMed PMID: 25257195; eng.
70. Yoo DH, Kim IS, Van Le TK, et al. Gut microbiota-mediated drug interactions between lovastatin and antibiotics. *Drug Metab Dispos*. 2014 Sep;42(9):1508-13. doi: 10.1124/dmd.114.058354. PubMed PMID: 24947972; eng.
71. Napolitano A, Miller S, Nicholls AW, et al. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. *PLoS ONE*. 2014;9(7):e100778. doi: 10.1371/journal.pone.0100778. PubMed PMID: 24988476; PubMed Central PMCID: PMC4079657. eng.
72. Vande Voorde J, Vervaeke P, Liekens S, et al. *Mycoplasma* hyorhinis-encoded cytidine deaminase efficiently inactivates cytosine-based anticancer drugs. *FEBS Open Bio*. 2015;5:634-9. doi: 10.1016/j.fob.2015.07.007. PubMed PMID: 26322268; PubMed Central PMCID: PMC4541722. eng.
73. Gonzalez-Sarrias A, Tome-Carneiro J, Bellesia A, et al. The ellagic acid-derived gut microbiota metabolite, urolithin A, potentiates the anticancer effects of 5-fluorouracil chemotherapy on human colon cancer cells. *Food Funct*. 2015 May;6(5):1460-9. doi: 10.1039/c5fo00120j. PubMed PMID: 25857357; eng.
74. Feng R, Shou JW, Zhao ZX, et al. Transforming berberine into its intestine-absorbable form by the gut microbiota. *Sci Rep*. 2015 Jul 15;5:12155. doi: 10.1038/srep12155. PubMed PMID: 26174047; PubMed Central PMCID: PMC4502414. eng.
75. Bang SH, Hyun YJ, Shim J, et al. Metabolism of rutin and poncirin by human intestinal microbiota and cloning of their metabolizing alpha-L-rhamnosidase from *Bifidobacterium dentium*. *J Microbiol Biotechnol*. 2015 Jan;25(1):18-25. PubMed PMID: 25179902; eng.
76. Sivan A, Corrales L, Hubert N, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015 Nov 27;350(6264):1084-9. doi: 10.1126/science.aac4255. PubMed PMID: 26541606; PubMed Central PMCID: PMC4873287. eng.
77. Wang D, Ho L, Faith J, et al. Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease beta-amyloid oligomerization. *Mol Nutr Food Res*. 2015 Jun;59(6):1025-40. doi: 10.1002/mnfr.201400544. PubMed PMID: 25689033; PubMed Central PMCID: PMC4498582. eng.
78. Yoo HH, Kim IS, Yoo DH, et al. Effects of orally administered antibiotics on the bioavailability of amlodipine: gut microbiota-mediated drug interaction. *J Hypertens*. 2016 Jan;34(1):156-62. doi: 10.1097/hjh.0000000000000773. PubMed PMID: 26630218; eng.
79. Song SC, An YM, Shin JH, et al. Beneficial effects of a probiotic blend on gastrointestinal side effects induced by leflunomide and amlodipine in a rat model. *Benef Microbes*. 2017 Oct 13;8(5):801-808. doi: 10.3920/bm2016.0231. PubMed PMID: 28969447; eng.
80. Klatt NR, Cheu R, Birse K, et al. Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women. *Science*. 2017 Jun 2;356(6341):938-945. doi: 10.1126/science.aai9383. PubMed PMID: 28572388; eng.
- ** A recent breakthrough discovery about the *Gardnerella*-dependent differential response of African women to the anti-HIV drug, tenofovir
81. Velazquez YF, Nacheva PM. Biodegradability of fluoxetine, mefenamic acid, and metoprolol using different microbial consortiums. *Environ Sci Pollut Res Int*. 2017 Mar;24(7):6779-6793. doi: 10.1007/s11356-017-8413-y. PubMed PMID: 28091995; eng.
82. Shen S, Lim G, You Z, et al. Gut microbiota is critical for the induction of chemotherapy-induced pain. *Nat Neurosci*. 2017 Sep;20(9):1213-1216. doi: 10.1038/nn.4606. PubMed PMID: 28714953; PubMed Central PMCID: PMC5575957. eng.
83. Yan A, Culp E, Perry J, et al. Transformation of the anticancer drug Doxorubicin in the human gut microbiome. *ACS Infect Dis*. 2018 Jan 12;4(1):68-76. doi: 10.1021/acsinfectdis.7b00166. PubMed PMID: 29160065; eng.
84. Biernat KA, Li B, Redinbo MR. Microbial unmasking of plant glycosides. *MBio*. 2018 Jan 30;9(1). doi: 10.1128/mBio.02433-17. PubMed PMID: 29382739; PubMed Central PMCID: PMC5790921. eng.

85. Zhang J, Chen Y, Sun Y, et al. Plateau hypoxia attenuates the metabolic activity of intestinal flora to enhance the bioavailability of nifedipine. *Drug Deliv.* 2018 Nov;25(1):1175-1181. doi: 10.1080/10717544.2018.1469687. PubMed PMID: 29790376; eng.
86. Gong S, Lan T, Zeng L, et al. Gut microbiota mediates diurnal variation of acetaminophen induced acute liver injury in mice. *J Hepatol.* 2018 Mar 8. doi: 10.1016/j.jhep.2018.02.024. PubMed PMID: 29524531; eng.
87. Mathan VI, Wiederman J, Dobkin JF, et al. Geographic differences in digoxin inactivation, a metabolic activity of the human anaerobic gut flora. *Gut.* 1989 Jul;30(7):971-7. PubMed PMID: 2759492; PubMed Central PMCID: PMC1434295. eng.
88. Dobkin JF, Saha JR, Butler VP, Jr., et al. Inactivation of digoxin by *Eubacterium lentum*, an anaerobe of the human gut flora. *Trans Assoc Am Physicians.* 1982;95:22-9. PubMed PMID: 7182977; eng.
89. Koppel N, Bisanz JE, Pandelia ME, et al. Discovery and characterization of a prevalent human gut bacterial enzyme sufficient for the inactivation of a family of plant toxins. *Elife.* 2018 May 15;7. doi: 10.7554/eLife.33953. PubMed PMID: 29761785; PubMed Central PMCID: PMC5953540. eng.
90. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science.* 2013 Nov 22;342(6161):971-6. doi: 10.1126/science.1240537. PubMed PMID: 24264990; eng.
** One of the best studied cases of drug-microbiome-immune system synergy against cancer. It sheds light on the complexity of events resulting from alteration of microbial composition in the gastrointestinal tract.
91. Haiser HJ, Turnbaugh PJ. Is it time for a metagenomic basis of therapeutics? *Science.* 2012 Jun 8;336(6086):1253-5. doi: 10.1126/science.1224396 [doi]. PubMed PMID: 22674325; eng.
92. Gilbert JA, Quinn RA, Debelius J, et al. Microbiome-wide association studies link dynamic microbial consortia to disease. *Nature.* 2016 Jul 7;535(7610):94-103. doi: 10.1038/nature18850. PubMed PMID: 27383984; eng.
* A suggested roadmap for designing and implementing microbiome-wide association studies in patient stratification towards precision medicine
93. Spanogiannopoulos P, Bess EN, Carmody RN, et al. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. *Nat Rev Microbiol.* 2016 Apr;14(5):273-87. doi: 10.1038/nrmicro.2016.17. PubMed PMID: 26972811; PubMed Central PMCID: PMC5243131. eng.
94. Patterson AD, Turnbaugh PJ. Microbial determinants of biochemical individuality and their impact on toxicology and pharmacology. *Cell Metab.* 2014 Nov 4;20(5):761-8. doi: 10.1016/j.cmet.2014.07.002. PubMed PMID: 25156450; PubMed Central PMCID: PMC4252706. eng.
95. Choi MS, Yu JS, Yoo HH, et al. The role of gut microbiota in the pharmacokinetics of antihypertensive drugs. *Pharmacol Res.* 2018 Jan 30. doi: 10.1016/j.phrs.2018.01.019. PubMed PMID: 29391236; eng.
96. Yi M, Yu S, Qin S, et al. Gut microbiome modulates efficacy of immune checkpoint inhibitors. *J Hematol Oncol.* 2018 Mar 27;11(1):47. doi: 10.1186/s13045-018-0592-6. PubMed PMID: 29580257; PubMed Central PMCID: PMC5870075. eng.
97. Alexander JL, Wilson ID, Teare J, et al. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat Rev Gastroenterol Hepatol.* 2017 Jun;14(6):356-365. doi: 10.1038/nrgastro.2017.20. PubMed PMID: 28270698; eng.
98. Bisanz JE, Spanogiannopoulos P, Pieper LM, et al. How to determine the role of the microbiome in drug disposition. *Drug Metab Dispos.* 2018 Aug 15. doi: 10.1124/dmd.118.083402. PubMed PMID: 30111623; eng.
99. Romano KA, Vivas EI, Amador-Noguez D, et al. Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide. *MBio.* 2015 Mar 17;6(2):e02481. doi: 10.1128/mBio.02481-14. PubMed PMID: 25784704; PubMed Central PMCID: PMC4453578. eng.
100. Rothhammer V, Borucki DM, Tjon EC, et al. Microglial control of astrocytes in response to microbial metabolites. *Nature.* 2018 May;557(7707):724-728. doi: 10.1038/s41586-018-0119-x. PubMed PMID: 29769726; eng.

101. Theilmann MC, Goh YJ, Nielsen KF, et al. *Lactobacillus acidophilus* metabolizes dietary plant glucosides and externalizes their bioactive phytochemicals. *MBio*. 2017 Nov 21;8(6). doi: 10.1128/mBio.01421-17. PubMed PMID: 29162708; PubMed Central PMCID: PMC5698550. eng.
102. Lin XB, Farhangfar A, Valcheva R, et al. The role of intestinal microbiota in development of irinotecan toxicity and in toxicity reduction through dietary fibres in rats. *PLoS ONE*. 2014;9(1):e83644. doi: 10.1371/journal.pone.0083644. PubMed PMID: 24454707; PubMed Central PMCID: PMC3891650. eng.
103. Kaiser J. Gut microbes shape response to cancer immunotherapy. *Science*. 2017 Nov 3;358(6363):573. doi: 10.1126/science.358.6363.573. PubMed PMID: 29097525; eng.
104. Dubin K, Callahan MK, Ren B, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. *Nat Commun*. 2016 Feb 2;7:10391. doi: 10.1038/ncomms10391. PubMed PMID: 26837003; PubMed Central PMCID: PMC4740747. eng.
105. Sun P, Chen JY, Li J, et al. The protective effect of geniposide on human neuroblastoma cells in the presence of formaldehyde. *BMC Complement Altern Med*. 2013 Jul 1;13:152. doi: 10.1186/1472-6882-13-152. PubMed PMID: 23815892; PubMed Central PMCID: PMC3702466. eng.
106. Khanal T, Kim HG, Choi JH, et al. Biotransformation of geniposide by human intestinal microflora on cytotoxicity against HepG2 cells. *Toxicol Lett*. 2012 Mar 25;209(3):246-54. doi: 10.1016/j.toxlet.2011.12.017. PubMed PMID: 22245672; eng.
107. Kodawara T, Higashi T, Negoro Y, et al. The inhibitory effect of ciprofloxacin on the beta-glucuronidase-mediated deconjugation of the irinotecan metabolite SN-38-G. *Basic Clin Pharmacol Toxicol*. 2016 May;118(5):333-7. doi: 10.1111/bcpt.12511. PubMed PMID: 26518357; eng.
108. Wallace BD, Roberts AB, Pollet RM, et al. Structure and inhibition of microbiome beta-glucuronidases essential to the alleviation of cancer drug toxicity. *Chem Biol*. 2015 Sep 17;22(9):1238-49. doi: 10.1016/j.chembiol.2015.08.005. PubMed PMID: 26364932; PubMed Central PMCID: PMC4575908. eng.
109. Kong R, Liu T, Zhu X, et al. Old drug new use--amoxapine and its metabolites as potent bacterial beta-glucuronidase inhibitors for alleviating cancer drug toxicity. *Clin Cancer Res*. 2014 Jul 1;20(13):3521-30. doi: 10.1158/1078-0432.ccr-14-0395. PubMed PMID: 24780296; PubMed Central PMCID: PMC4079752. eng.
110. Geller LT, Straussman R. Intratumoral bacteria may elicit chemoresistance by metabolizing anticancer agents. *Mol Cell Oncol*. 2018;5(1):e1405139. doi: 10.1080/23723556.2017.1405139. PubMed PMID: 29404397; PubMed Central PMCID: PMC5791857. eng.
111. Geller LT, Barzily-Rokni M, Danino T, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science*. 2017 Sep 15;357(6356):1156-1160. doi: 10.1126/science.aah5043. PubMed PMID: 28912244; eng.
112. Zhang L, Xie C, Nichols RG, et al. Farnesoid X receptor signaling shapes the gut microbiota and controls hepatic lipid metabolism. *mSystems*. 2016 Sep-Oct;1(5). doi: 10.1128/mSystems.00070-16. PubMed PMID: 27822554; PubMed Central PMCID: PMC5080402. eng.
113. Gao B, Chi L, Mahbub R, et al. Multi-omics reveals that lead exposure disturbs gut microbiome development, key metabolites, and metabolic pathways. *Chem Res Toxicol*. 2017 Apr 17;30(4):996-1005. doi: 10.1021/acs.chemrestox.6b00401. PubMed PMID: 28234468; PubMed Central PMCID: PMC5654721. eng.
114. Nichols D, Cahoon N, Trakhtenberg EM, et al. Use of ichip for high-throughput in situ cultivation of "uncultivable" microbial species. *Appl Environ Microbiol*. 2010 Apr;76(8):2445-50. doi: 10.1128/aem.01754-09. PubMed PMID: 20173072; PubMed Central PMCID: PMC2849220. eng.
115. Tanaka T, Kawasaki K, Daimon S, et al. A hidden pitfall in the preparation of agar media undermines microorganism cultivability. *Appl Environ Microbiol*. 2014 Dec;80(24):7659-66. doi: 10.1128/aem.02741-14. PubMed PMID: 25281372; PubMed Central PMCID: PMC4249246. eng.
116. Penalver Bernabe B, Cralle L, Gilbert JA. Systems biology of the human microbiome. *Curr Opin Biotechnol*. 2018 Jun;51:146-153. doi: 10.1016/j.copbio.2018.01.018. PubMed PMID: 29453029; eng.