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The Gut Microbiome and Pharmacology: A Prescription for Therapeutic Targeting of the Gut-Brain Axis

Pauline Leprun[1,2,3], Gerard Clarke [1,2,4*]

[1] Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork Ireland

[2] APC Microbiome Ireland, University College Cork, Cork, Ireland

[3] University of Rennes 1, Rennes, France

[4] INFANT Research Centre, University College Cork, Cork, Ireland

*Corresponding author: Dr Gerard Clarke, Department of Psychiatry and Neurobehavioural Science and APC Microbiome Ireland, 1.15 Biosciences Building, University College Cork, Cork, Ireland

Tel + 353 21 4901408
Fax + 353 21 4901722
g.clarke@ucc.ie

Abstract

New frontiers for host-microbe interactions continue to emerge as our knowledge of the adult gut microbiome in health and disease is continually supplemented and improved. Alterations in the gut microbiota composition in irritable bowel syndrome (IBS) are now linked to symptom severity while population based evidence linking gut microbiome signatures to depression is an important new landmark. The effects of drugs on gut microbiome composition is also becoming clearer. Meanwhile, preclinical studies have delineated the influence of the gut microbiome at a structural and activity level in distinct brain regions. Bacterial metabolites, such as tryptamine, can activate specific receptors to impact gastrointestinal motility. These recent studies bring into focus the future implications for therapeutic targeting of the microbiome-gut-brain axis.

Introduction

As our knowledge of the important role played by the gut microbiota in health and disease expands, new frontiers for host-microbe interactions continue to emerge. Recently, traditional concepts in pharmacology and therapeutics have been challenged by reports outlining reciprocal microbiome-xenobiotic interactions and a growing appreciation that microbial metabolites might exert their effects via receptor-mediated mechanisms. In this review, we first outline the most salient aspects of the composition and function of the gut microbiome as a framework to understand the importance of this virtual organ for gastrointestinal pharmacology and beyond. We then focus on a number of key recently published articles illustrating the implications of important conceptual advances that chart the scope and scale of microbial regulation of pharmacodynamics and pharmacokinetics in the gut-brain axis. This is considered within the context of the bidirectional relationship between xenobiotics and our gut bacteria. Finally, we attempt to integrate these observations to elaborate on the future implications for therapeutic targeting of the microbiome-gut-brain axis.

The Adult Gut Microbiome: A Metabolic Powerhouse

The adult gut microbiota is made up of trillions of microorganisms (bacteria, viruses, archaea, yeasts and fungi) that reside in the gastrointestinal tract, contributing substantially to host physiological homestasis. The community of bacteria is best studied with the highest density in the large intestine which according to recent estimates reaches 10^{13} bacterial cells in the human colon [1,2]. The composition and function of this complex bacterial ecosystem is individual –specific and impacted by a number of intrinsic and extrinsic factors, including diseases and drug use, diet, age and lifestyle of the host [3-5]. Recent sequencing surveys confirm that the adult gut microbiota is dominated from a compositional perspective by the phyla *Firmicutes*, *Actinobacteria* and *Bacteroidetes* with lower relative abundances of *Verrucomicrobia* and *Proteobacteria*. There may also be a core microbiota defined by 14 different genera with medication use in general contributing to microbiota compositional variation [3]. Our knowledge of the complexity of this virtual organ continues to expand and through the use of sequencing approaches, metagenomic analysis and bioinformatic pipelines. Pasolli and colleagues [6] have recently elegantly revealed the presence of new microbial species on or in the host, including the gut, associated with westernized or non-westernized lifestyles. In addition, many newly identified species-level operational taxonomic

units (OTUs) may be associated with disease states as their genome sequences were not previously captured in databases [7].

The aggregate genome of this community, the metagenome, far exceeds and complements the metabolic capacity of the host genome. These microbial genes encode an array of metabolic activities, providing the host with additional essential functional capacity, such as the digestion of dietary fibers, which yields microbial metabolites important for host-microbe interactions. All these recent reports continue to support the importance of the gut microbiota in human health, although there remains knowledge gaps surrounding the precise composition of a healthy gut microbiome across the life span and more granular details on the molecular mechanisms underpinning complex host-microbe interactions, particularly in the context of gastrointestinal pharmacology.

The Gut Microbiome in Disease

Shifts in the bacterial composition, structure or function in the gastrointestinal tract have been associated with numerous disorders in the last few decades. As studies go beyond microbial surveys, the quality of the information derived from these studies continues to improve. For example, it now appears that alterations in the gut microbiota composition in irritable bowel syndrome (IBS) may include microbiota signatures associated with symptom severity [8]. In particular, IBS symptom severity was negatively associated with microbial richness as well as the presence of methanogens, and gut microbiota enterotypes characterized by enriched *Clostridiales* or *Prevotella* species [8]. This confirms the importance for the gut microbiota in the development of functional gastrointestinal disorders as well as chronic inflammatory diseases (see [9]).

With the increasing number of studies focused on the gut microbiota and mental health, compositional alterations have also been highlighted in psychiatric and neurological disorders, such as Alzheimer's disease [10], Parkinson's disease [11,12], autism spectrum disorders (ASD) [13], schizophrenia [14] and depression [15]. In many cases, a causal role for these disease-associated microbiome configurations can be inferred from the transfer of behavioural phenotypes to animal models via the microbiota [15,16]. In the case of IBS, this even extends to the transfer of specific psychiatric comorbidities such as anxiety [16]. More recently, the analysis of a large microbiome population cohort enabled the identification of *Dialister* and *Coprococcus* spp as indicators of high quality of life, and revealed their depletion in depressive patients [17]. The results of this study

have advanced our knowledge further, providing the first population based evidence linking gut microbiome compositional signatures with a mental health disorder. It is therefore becoming increasingly important to consider the intestinal microbiota as a biomarker reservoir, in the development of new treatments and as a source of the side effects associated with particular host-directed medications.

--- Insert Figure 1 Here ---

The Gut Microbiome and Expanding array of Therapeutic Targets in the Gut-brain Axis:

While microbial signatures or alterations in the composition of the microbiota now appear to be evident in various pathologies, the extent of, and mechanisms involved in, this communication remain to be fully grasped. A variety of preclinical approaches, including the use of germ-free animals (GF), have allowed the scope of influence of the enteric microbiota on the brain-gut axis to be defined. Abdominal pain, underpinned by visceral hypersensitivity, is a core feature of irritable bowel syndrome (IBS). Recently, it has been conclusively demonstrated that the gut microbiota is required for normal visceral pain sensation, associated with increases in toll-like receptor and cytokine gene expression in the spinal cord. This study also demonstrated that the volumes of brain regions involved in pain processing such as the anterior cingulate cortex (ACC) and periaqueductal grey, were decreased and enlarged respectively in GF mice. [18]. This is consistent with previous studies which have demonstrated that the visceral hypersensitivity of IBS patients can be transferred to GF rats via the fecal microbiota [19].

Microbial regulation of the transcriptional activity in different brain areas, such as amygdala, prefrontal cortex or hippocampus, is now supported by several studies and often occurs in a sex-dependent manner [20-22]. Studies in GF animals also now implicate the gut microbiome in appropriate regulation of microRNA (miRNAs; non coding RNAs that act through translational repression to control gene expression) expression in brain regions implicated in anxiety-like behaviours such as the amygdala and prefrontal cortex [22] or in memory and learning, such as the hippocampus [21,23]. For instance, in the absence of a gut microbiota, the basal expression of specific activity-related genes in the amygdala is altered, leading to the suggestion that a hyperactivity of this brain structure might be at the root of the behavioural abnormalities associated with growing up germ free [24-27]. Whether this can be exploited therapeutically is an open

question but in support of this possibility, the behavioural consequences as well as the molecular signature of his hyperactivity can at least partially be reversed by the colonization of GF animals [25]. Of further interest is that fecal miRNAs of host or plant origin may have an important role in dictating microbiota composition, possibly by targeting regions in bacterial metagenomes [27-30] while fecal miRNA expression is also linked to gut microbiota fluctuations [31].

A recent study, based on a mouse model of autism (BTBR mice), highlighted a significant decrease of two bile-metabolizing species: *Bifidobacterium* and *Blautia*. Moreover, this compositional shift was associated with deficient bile acid and tryptophan metabolism, gastrointestinal dysfunction and impaired social interactions [32]. These results support the concept that modulation of the gut microbiota could be a promising strategy for the treatment of brain-gut axis disorders. In this context, Burokas and his team assessed the effect of the administration of two prebiotics in a rodent study: the gluco- and the fructo-oligosaccharides (GOS and FOS). Besides modifying the expression of genes such as BDNF in the hippocampus, GOS and FOS also exerted anxiolytic and antidepressant effects and reversed the behavioral and physiological impact of chronic stress exposure [33]. The finer details of the mechanisms mediating these beneficial effects remains unclear in many cases but substantial progress has been made in this area, particularly in the context of pharmacodynamic interactions between microbial metabolites and the host.

The Gut Microbiome and Pharmacodynamics

Bacterial metabolites are considered likely to be key mediators of these host microbe interactions with the possibility they can induce host cellular responses via their activity at G-protein-coupled receptors (GPCRs) expressed either locally in the gastrointestinal tract or at more distal locations [34]. One such example is tryptamine (a monoamine similar to 5-hydroxytryptamine (5-HT)), metabolized by bacteria via tryptophan decarboxylation, which modulate colonic secretion via activation of the 5-HT4 receptor (5-HT4R), a 5-HT receptor expressed in the colon of importance for regulation of gastrointestinal motility [35-37]. Another receptor of importance in this regard is the aryl hydrocarbon receptor (AhR) and a reduction of the microbiota's ability to metabolize tryptophan into ligands capable of activating this has been identified in metabolic syndrome [38] and colitis [39], supporting the importance of this bacterial product in receptor-mediated host homeostasis.

In other cases, microbial metabolites may alter the expression of key receptors to influence gastrointestinal function. The most studied metabolites produced by gut bacteria are the short chain fatty acids (SCFAs), derived from the fermentation of dietary fibers. For example, acetate production can regulate the expression of 5-HT3 receptor expression to influence host secretory patterns [36]. Beyond intestinal-located interactions and although well known for their direct interactions with the free fatty acid receptor (FFAR) 2 and 3 in the regulation of appetite and energy intake, SCFA supplementation has recently been associated with antidepressant and anxiolytic effects in mice. These effects were not present following exposure to a psychosocial stressor but the SCFA treatment did alleviate stress-induced increases in intestinal permeability while the stress-induced alterations in colonic gene expression of the SCFA receptors free fatty acid receptors were unaffected by SCFA supplementation [40].

The gut microbiota can also secrete compounds able to translocate from the gut to the systemic circulation, and to subsequently cross the blood-brain barrier. This applies to bacterial peptidoglycan (PGN), a major component of the bacterial membrane, which is able to activate neuronal pattern-recognition-receptors (PRR), leading to modulation of brain development during specific time windows, through an interaction with Pglyrp2 [41]. A deeper understanding of the functional implications and regulation of bacterial-products could then constitute a relevant strategy for modulating host homeostasis, and potentially the development of new therapies in a wide range of gut-brain axis disorders.

The Gut Microbiome, Pharmacokinetics and Toxicity

The study of pharmacokinetics has traditionally focused on the impact of the host on administered drugs without due regard for the functional capacity of the gut microbiota. Orally administrated drugs in particular represent a potential substrate for bacterial metabolism, which can lead to intrapersonal variations in drug availability, efficacy or toxicity. One of the prospective drugs for such a transformation was the immunosuppressant mycophenolate mofetil (MMF), which, despite its effectiveness, induces significant side effects. Nevertheless, treating GF mice with MMF showed significantly reduced side effects [42], strongly implicating the gut microbiota in the emergent adverse effects.

The bacteria inhabiting our gut have at their disposal a range of microbial enzymes able to modify drugs and other xenobiotics. Tyrosine decarboxylase (TDC), expressed in particular by *Enterococcus* and *Lactobacillus*, was pointed out for its ability to interfere in the treatment of Parkinson's disease through the inactivation of levodopa (L-DOPA) [43]. Moreover, it seems like prolonged treatment with L-DOPA enhances *tdc* gene expression, leading to a less and less effective treatment over time. *F. Prauznitzii* and *Clostridiales*, other specific enteric bacteria, have also been involved in the decrease of effectiveness of the immunosuppressant tacrolimus [44], highlighting the potential negative effect of gut microbiota on an orally administered medical treatment. In a similar vein, a bioinformatic approach enabled the identification of tyramine oxidase expressed by *E. Coli* as capable of binding amphetamine, leading to a potential modification of the drug [45]. Together, these results substantiate the relevance of using new models in pharmacology, that take into consideration microbial metabolism and the associated intra-individual variations. After an adaptation for other xenobiotics, the pharmacokinetic model built by Zimmermann and his team would hence represent an interesting basis to separate host and microbiome contributions to pharmacokinetics and toxicity [46].

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Effects of drugs on the gut microbiome

While, as shown above, the microbiota can have negative effects on the pharmacological properties of drugs, the reverse pattern is also valid: a large number of host-directed drugs across therapeutic classes combined, can affect the bacterial growth of at least 1 strain *in vitro* [47]. Psychotropic drugs have been particularly highlighted for their antimicrobial effects, causing alterations of the microbiota as well as modifications of gastrointestinal function such as intestinal permeability *in vivo*, and impacting on bacterial growth *in vitro* (Table 1) [48,49]. Earlier studies indicated that olanzapine altered the composition of the gut microbiota [50]. Further studies focusing on this drug showed that the microbiota was needed for drug-associated weight gain, a serious and common side effect of this antipsychotic treatment [51], as antibiotics attenuated the side effects in mice. This was also true in germ-free animals and olanzapine has antimicrobial effects on the growth of *E. Coli* and *Enterococcus faecalis in vitro* [52]. This opens up the possibility of targeting the gut microbiota with, for example, prebiotics to try and limit these adverse side effects [53].

Alternative approaches allowing the modulation of the enteric microbiota, such as fecal microbiota transplant (FMT), might also lend themselves to counterbalance, or at least limit, these adverse effects or indeed promote beneficial effects. Interestingly, the ketogenic diet (KD) which is used to treat refractory epilepsy, appears to induce alterations in the microbiota which are necessary for its anti-seizure effects [54]. Together with the FODMAP diet for control of IBS symptoms [55], this is an example of a diet of reduced diversity which would not normally be considered beneficial for our gut microbes but which produce symptomatic improvements in the host. According to our current knowledge of the gut microbiota and host-microbe interactions within the framework of pharmacokinetics and pharmacodynamics, the effects of a wide range of host-directed xenobiotics on our bacteria community has to be more routinely considered in drug development pipelines.

Conclusion

Recent research has aided substantially our efforts to make sense of the microbiome-gut-brain axis in gastrointestinal pharmacology and beyond. This includes advances over compositional surveys to important studies linking symptom severity to gut microbiome alterations in IBS, as well as landmark population based evidence linking gut microbiome signatures to depression and quality of life. Moreover, the increase in research linking the gut microbiome to neuropsychiatric disorders from clinical studies is supplemented with preclinical approaches that implicate the gut microbiome in regulating even the structure and activity of key brain regions. Meanwhile, traditional concepts in pharmacology will likely need to be redrawn to account for the reciprocal interactions between our gut microbes and xenobiotics. This will have important implications for pharmacodynamics and pharmacokinetic considerations during drug development. Our understanding of the molecular mediators underpinning host-microbe interactions now includes an appreciation that microbial metabolites can impact on specific receptors to influence aspects of host physiology such as gastrointestinal motility. It remains an appealing prospect that this knowledge can be harnessed effectively for therapeutic targeting of the microbiome to influence gut-brain axis signaling using interventions such as FMT, prebiotics, probiotics or postbiotics. Limiting the side effects associated with psychotropic drugs such as antipsychotics via microbiome-based approaches is a further avenue of investigation with high potential. Effectively translating these promising recent advances into the prescription pads of the future is an ambitious but important research objective.

Conflict of Interest

APC Microbiome Ireland collaborates with a number of industry partners including Dupont Nutrition Biosciences APS, Cremo SA, Alkermes Inc., 4D Pharma PLC, Mead Johnson Nutrition, Nutricia Danone and Suntory Wellness. GC has spoken at meetings sponsored by food and pharmaceutical companies including Janssen Ireland. This neither influenced nor constrained the content of this review.

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Figure Legends

Figure 1: The Microbiome-gut-brain axis and Psychiatry

The composition of the gut microbiome is under the influence of various intrinsic and extrinsic factors, such as the host genetics, age, and other lifestyle factors. The gut microbiome can recruit the gut-brain axis, a bidirectional communication system between the brain and the gut, to influence brain function and behaviour. Alterations in the composition and function of the gut microbiome have been associated with a number of clinical psychiatric and neurological disorders while preclinical approaches confirm the capacity of our gut microbes to exert behavioural and functional effects of relevance to these brain disorders. Psychological stress exposure can also impact on the structure and function of the gut microbiome.

Figure 2: Xenobiotics and Gut Microbiota Interactions

Orally administrated drugs are, after ingestion, in direct contact with the gut microbiome. The co-localization of bacteria and xenobiotics may result in reciprocal interactions. On one hand, many xenobiotics have antimicrobial properties and can alter microbiota composition, diversity and function, often in a manner that can be linked to the side effects of various medications. On the other hand, the gut microbiota can metabolize the ingested drugs or indirectly alter their metabolism by the host and this can result modification of availability, efficacy or toxicity of the drug in the organism. Many disease states are also associated with gut microbiome alterations, even prior to drug use although the implication of this are currently unclear.

Table 1: Psychotropic drugs and their effects on the gut microbiome and intestinal physiology in preclinical studies

Drug	Disease	Observed effects	Reference
Aripiprazole	Schizophrenia, major depression, bipolar disorder, obsessive- compulsive disorder	↑ bacterial richness and diversity ↑ Firmicutes ↑ the levels of acetate and isovalerate ↑ distal ileum permeability	[48]
		↓ *E. Coli* IAI1 & *L. gasseri*	[56]
Escitalopram	Depression/anxiety disorders	↓ *E. Coli* growth *invitro* ↑ distal ileum permeability	[48]
Fluoxetine	Depression/anxiety disorders	Inhibit *L. rhamnosus* and *E. Coli* growth ↓ *Deferribacteraceae* ↑ distal ileum permeability	[48]
		↑ *Firmicute*/*Bacteroidete* ratio	[49]
Lithium	Bipolar disorder, mood-stabilizer, major depression, schizophrenia	↑ bacterial richness and diversity ↑ *Actinobacteria* et diminution *Bacteroidetes*	[48]
Olanzapine	Schizophrenia, bipolar disorder	↑ level of *Firmicute* and ↓ bacterial diversity in females ↓ *Proteobacteria* in males ↓ *Bacteroidetes*	[50]
		↑ *Firmicutes* and ↓ *Bacteroidetes*	[51]
		↓ E. Coli and Enterococcus faecalis croissance in vitro	[52]
Valproate	Epilepsy, bipolar disorder, schizophrenia	↑ bacterial richness and diversity ↑ Actinobacteria and Firmicute - ↓ Bacteroidete ↓ propionate and butyrate levels and ↑ isovalerate	[48]
Venlafaxine	Depressive/anxiety disorders	↑ distal ileum permeability	[48]

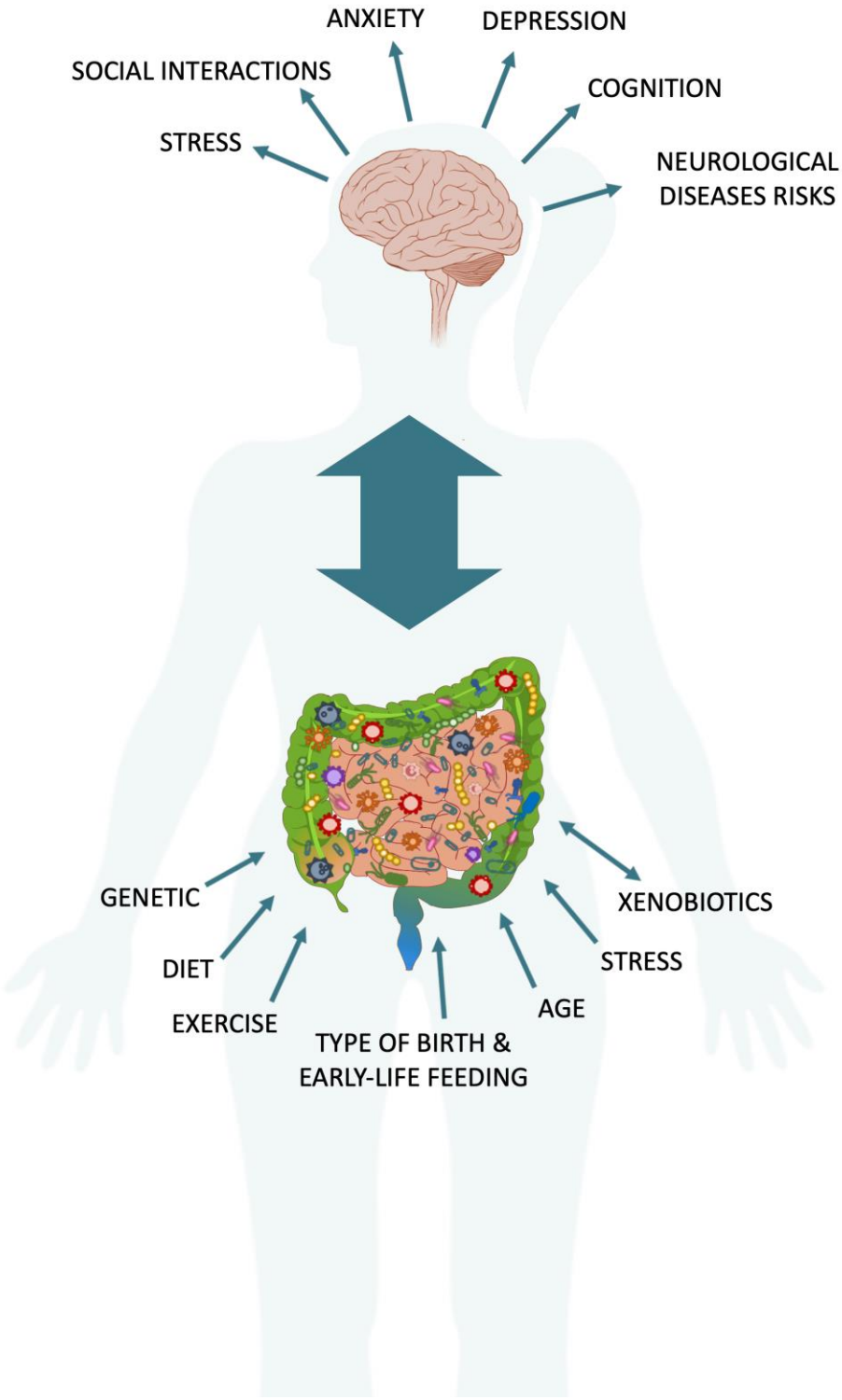

ANXIETY
DEPRESSION
SOCIAL INTERACTIONS
COGNITION
STRESS
NEUROLOGICAL
DISEASES RISKS
GENETIC
XENOBIOTICS
DIET
STRESS
EXERCISE
AGE
TYPE OF BIRTH &
EARLY-LIFE FEEDING

Figure 1

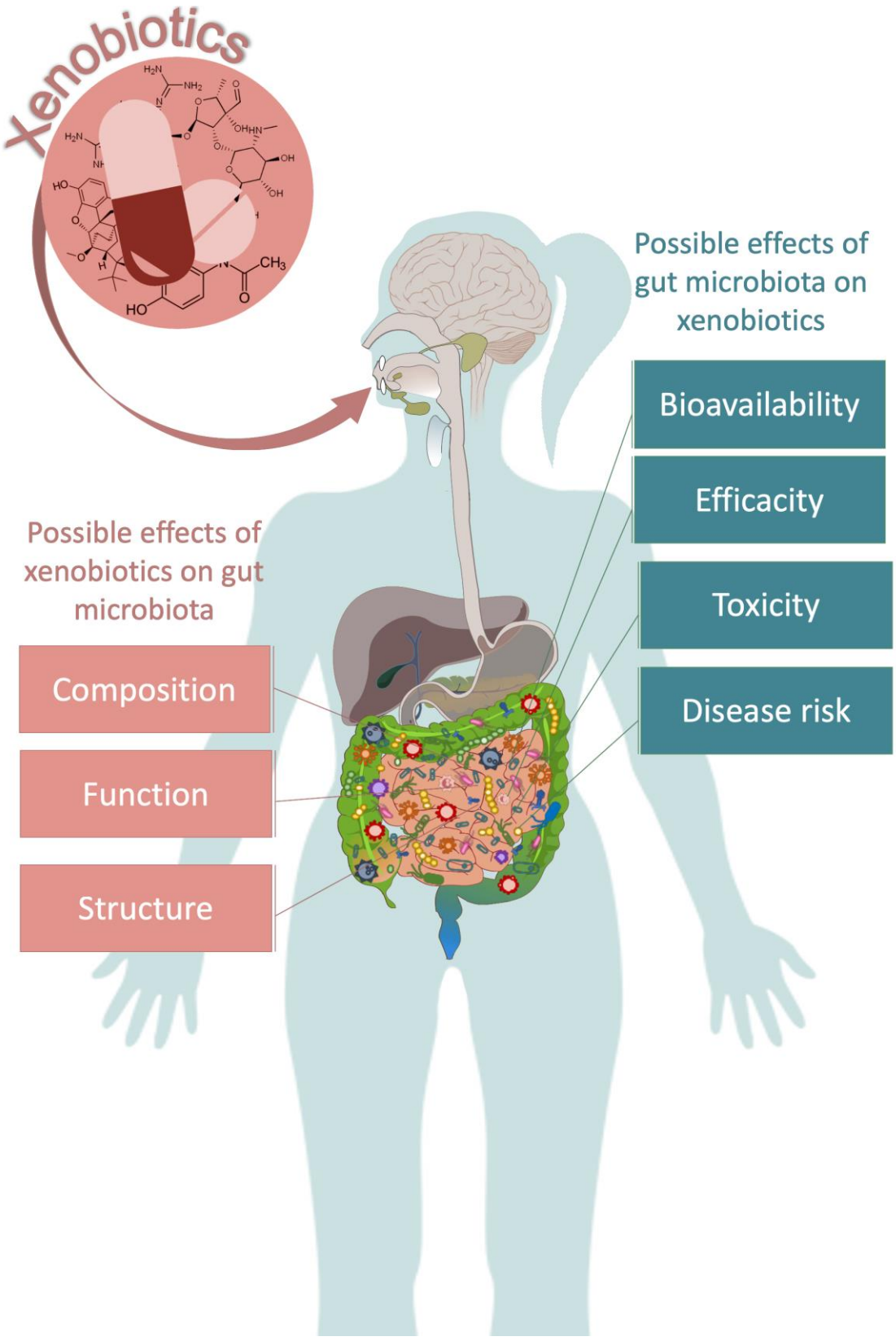

Xenobiotics
Possible effects of gut microbiota on xenobiotics
Bioavailability
Efficacity
Toxicity
Disease risk
Possible effects of xenobiotics on gut microbiota
Composition
Function
Structure

Figure 2