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

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Abstract

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

26

27

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

42 **The Adult Gut Microbiome: A Metabolic Powerhouse**

43 The adult gut microbiota is made up of trillions of microorganisms (bacteria, viruses, archaea,
44 yeasts and fungi) that reside in the gastrointestinal tract, contributing substantially to host
45 physiological homeostasis. The community of bacteria is best studied with the highest density in the
46 large intestine which according to recent estimates reaches 10^{13} bacterial cells in the human colon
47 [1,2]. The composition and function of this complex bacterial ecosystem is individual –specific
48 and impacted by a number of intrinsic and extrinsic factors, including diseases and drug use, diet,
49 age and lifestyle of the host [3-5]. Recent sequencing surveys confirm that the adult gut microbiota
50 is dominated from a compositional perspective by the phyla *Firmicutes*, *Actinobacteria* and
51 *Bacteroidetes* with lower relative abundances of *Verrucomicrobia* and *Proteobacteria*. There may
52 also be a core microbiota defined by 14 different genera with medication use in general contributing
53 to microbiota compositional variation [3]. Our knowledge of the complexity of this virtual organ
54 continues to expand and through the use of sequencing approaches, metagenomic analysis and
55 bioinformatic pipelines. Pasolli and colleagues [6] have recently elegantly revealed the presence of
56 new microbial species on or in the host, including the gut, associated with westernized or non-
57 westernized lifestyles. In addition, many newly identified species-level operational taxonomic

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

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

69

70 **The Gut Microbiome in Disease**

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

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

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

94

95

--- Insert Figure 1 Here ---

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

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

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

119 question but in support of this possibility, the behavioural consequences as well as the molecular
120 signature of his hyperactivity can at least partially be reversed by the colonization of GF animals
121 [25]. Of further interest is that fecal miRNAs of host or plant origin may have an important role in
122 dictating microbiota composition, possibly by targeting regions in bacterial metagenomes [27-30]
123 while fecal miRNA expression is also linked to gut microbiota fluctuations [31].

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

136 **The Gut Microbiome and Pharmacodynamics**

137 Bacterial metabolites are considered likely to be key mediators of these host microbe interactions
138 with the possibility they can induce host cellular responses via their activity at G-protein-coupled
139 receptors (GPCRs) expressed either locally in the gastrointestinal tract or at more distal locations
140 [34]. One such example is tryptamine (a monoamine similar to 5-hydroxytryptamine (5-HT)),
141 metabolized by bacteria via tryptophan decarboxylation, which modulate colonic secretion via
142 activation of the 5-HT₄ receptor (5-HT₄R), a 5-HT receptor expressed in the colon of importance
143 for regulation of gastrointestinal motility [35-37]. Another receptor of importance in this regard is
144 the aryl hydrocarbon receptor (AhR) and a reduction of the microbiota's ability to metabolize
145 tryptophan into ligands capable of activating this has been identified in metabolic syndrome [38]
146 and colitis [39], supporting the importance of this bacterial product in receptor-mediated host
147 homeostasis.

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

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

167 **The Gut Microbiome, Pharmacokinetics and Toxicity**

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

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

191 --- Insert Figure 2 Here ---

192 **Effects of drugs on the gut microbiome**

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

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

215 **Conclusion**

216
217 Recent research has aided substantially our efforts to make sense of the microbiome-gut-brain axis
218 in gastrointestinal pharmacology and beyond. This includes advances over compositional surveys
219 to important studies linking symptom severity to gut microbiome alterations in IBS, as well as
220 landmark population based evidence linking gut microbiome signatures to depression and quality
221 of life. Moreover, the increase in research linking the gut microbiome to neuropsychiatric disorders
222 from clinical studies is supplemented with preclinical approaches that implicate the gut microbiome
223 in regulating even the structure and activity of key brain regions. Meanwhile, traditional concepts
224 in pharmacology will likely need to be redrawn to account for the reciprocal interactions between
225 our gut microbes and xenobiotics. This will have important implications for pharmacodynamics
226 and pharmacokinetic considerations during drug development. Our understanding of the molecular
227 mediators underpinning host-microbe interactions now includes an appreciation that microbial
228 metabolites can impact on specific receptors to influence aspects of host physiology such as
229 gastrointestinal motility. It remains an appealing prospect that this knowledge can be harnessed
230 effectively for therapeutic targeting of the microbiome to influence gut-brain axis signaling using
231 interventions such as FMT, prebiotics, probiotics or postbiotics. Limiting the side effects associated
232 with psychotropic drugs such as antipsychotics via microbiome-based approaches is a further
233 avenue of investigation with high potential. Effectively translating these promising recent
234 advances into the prescription pads of the future is an ambitious but important research objective.

235 **Conflict of Interest**

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

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246

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496 **Figure Legends**

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

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

508

509 **Figure 2: Xenobiotics and Gut Microbiota Interactions**

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

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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	[48]
		↑ Firmicutes ↑ the levels of acetate and isovalerate ↑ distal ileum permeability	
Escitalopram	Depression/anxiety disorders	↓ <i>E. Coli</i> growth <i>invitro</i>	[48]
		↑ distal ileum permeability	
Fluoxetine	Depression/anxiety disorders	Inhibit <i>L. rhamnosus</i> and <i>E. Coli</i> growth	[48]
		↓ <i>Deferribacteraceae</i> ↑ distal ileum permeability	
Lithium	Bipolar disorder, mood-stabilizer, major depression, schizophrenia	↑ <i>Firmicute/Bacteroidete</i> ratio	[49]
		↑ bacterial richness and diversity ↑ <i>Actinobacteria</i> et diminution <i>Bacteroidetes</i>	[48]
Olanzapine	Schizophrenia, bipolar disorder	↑ level of <i>Firmicute</i> and ↓ bacterial diversity in females	[50]
		↓ <i>Proteobacteria</i> in males	
		↓ <i>Bacteroidetes</i>	[51]
		↑ <i>Firmicutes</i> and ↓ <i>Bacteroidetes</i>	
Valproate	Epilepsy, bipolar disorder, schizophrenia	↓ <i>E. Coli</i> and <i>Enterococcus faecalis</i> croissence in vitro	[52]
		↑ bacterial richness and diversity ↑ <i>Actinobacteria</i> and <i>Firmicute</i> - ↓ <i>Bacteroidete</i> ↓ propionate and butyrate levels and ↑ isovalerate	[48]
Venlafaxine	Depressive/anxiety disorders	↑ distal ileum permeability	[48]

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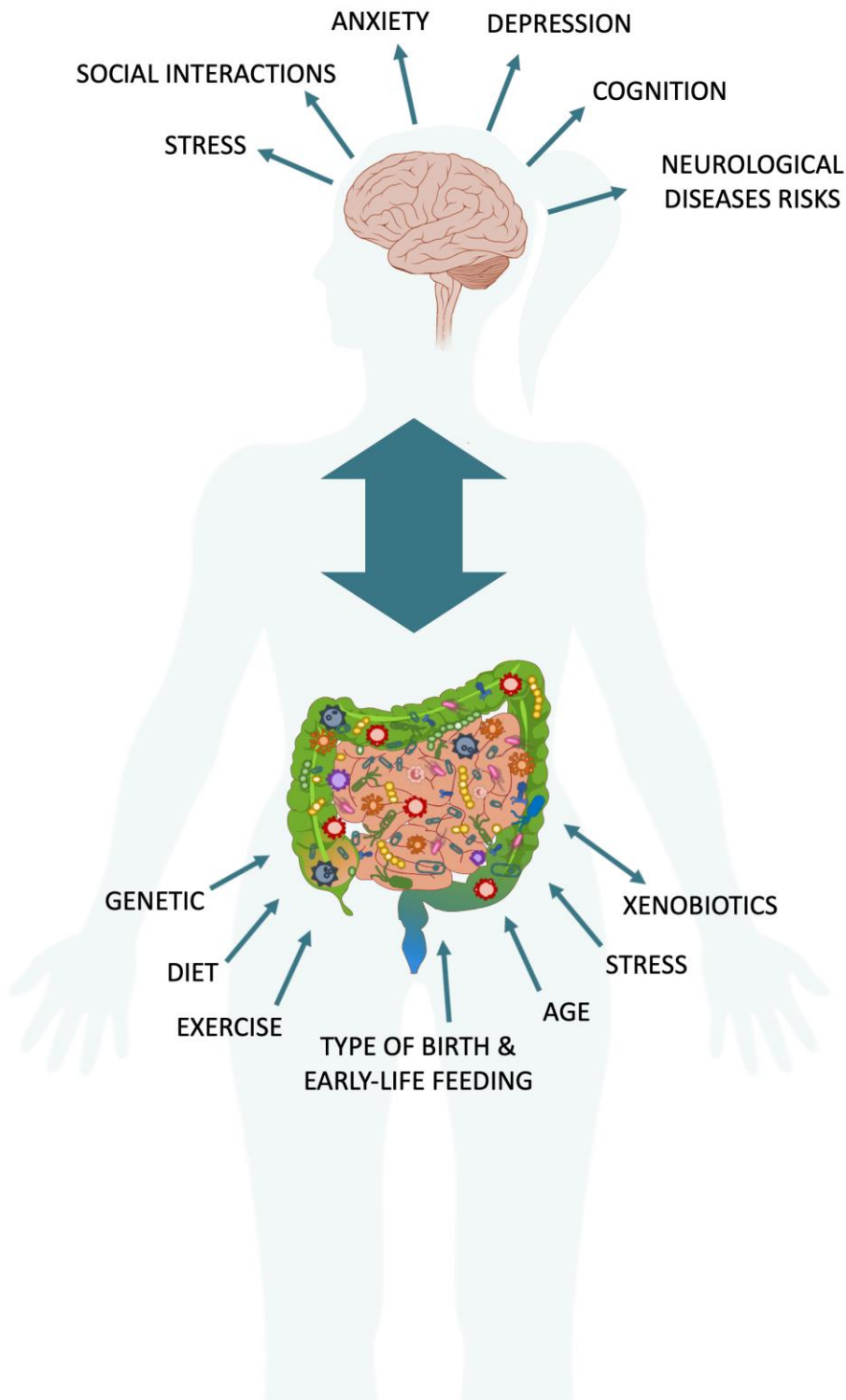


Figure 1

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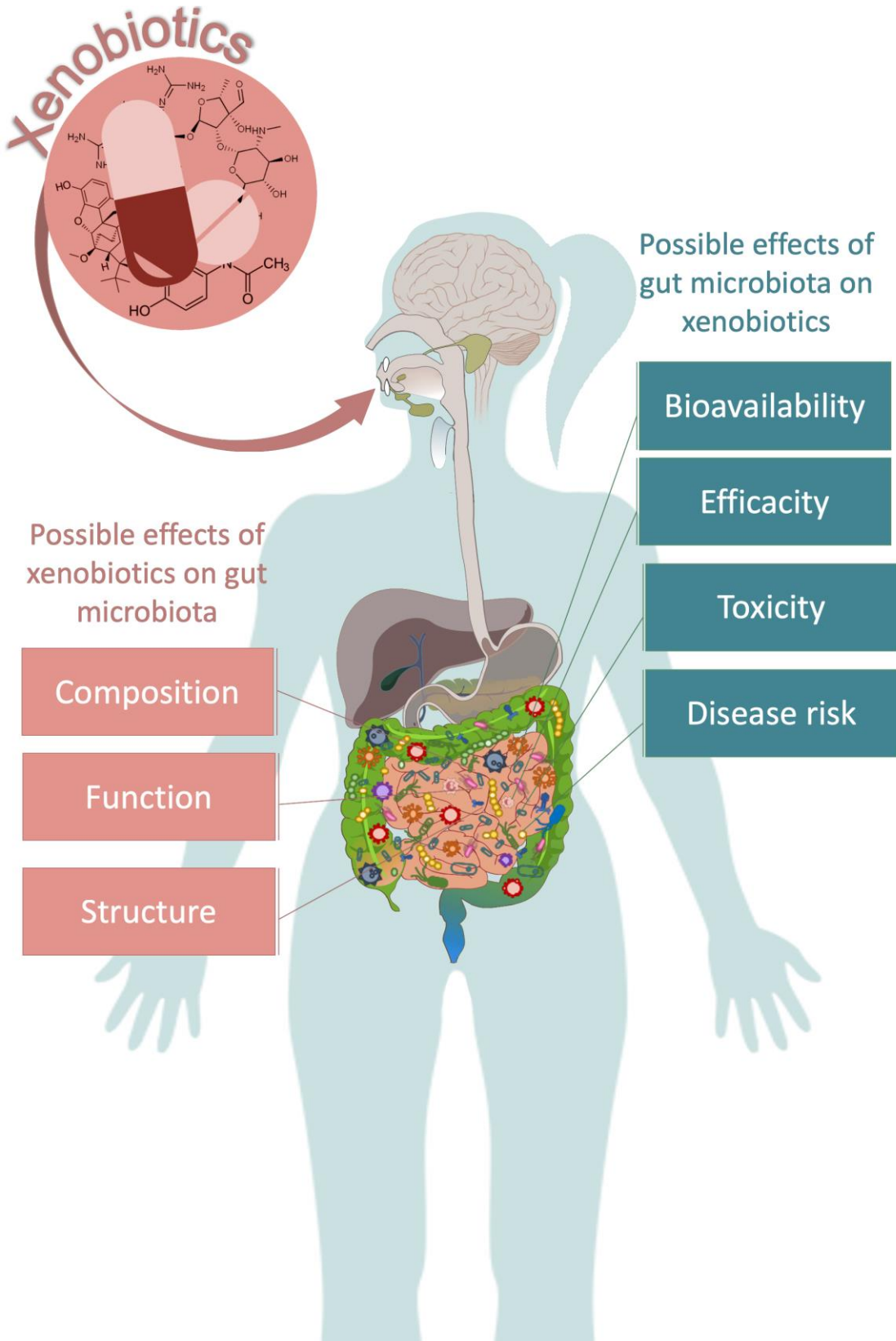


Figure 2