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The Role of the Gut Microbiota in the Metabolism of Polyphenols as Characterized by Gnotobiotic Mice

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Abstract

A growing body of experimental data suggests that microbes in the gut influence behavior and can alter brain physiology and neurochemistry. Although promising, researchers are only starting to understand the potential of the gut microbiota for use in neurological disease. Recent evidence demonstrated that gastrointestinal activities are linked to mood disorders such as anxiety, depression, and most recently, cognitive functions in age-related neurodegenerative disorders. Studies from our group and others are uncovering new evidence suggesting that the gut microbiota plays a crucial role in the metabolism and bioavailability of certain dietary compounds and synthetic drugs. Based on this evidence, this review article will discuss the implications of the gut microbiota in mechanisms of bioavailability and biotransformation with an emphasis on dietary polyphenol compounds. This will be followed by a survey of ongoing innovative research identifying the ability of individual gut bacteria to enhance the bioavailability of gut-derived, brain-penetrating, bioactive polyphenol metabolites that ultimately influence mechanisms associated with the promotion of resilience against psychological and cognitive impairment in response to stress. Lastly, current research initiatives aimed at promoting the generation of brain bioactive polyphenol metabolites by specialized gut microbes will be discussed, specifically the use of gnotobiotic mice to develop bioengineered second generation probiotics. We propose that leveraging the gut microbial ecosystem to generate brain targeted bioactive metabolites from dietary polyphenols can attenuate lifestyle risk factors and promote resilience against age-related cognitive decline.

Keywords

Gnotobiotic mice; inflammation; microbiota; oxidative stress; polyphenol metabolism

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INTRODUCTION

In recent years, the scientific community has begun to understand the intricate and dynamic interactions between the symbiotic bacteria in the gastrointestinal (GI) tract, the gut microbiota, and neurological function [1–8]. The bacteria of the gut have been show to affect high order cognition and physiological functions and they are crucial to physiological homeostasis [9–14]. Ongoing studies support the hypothesis that the gut microbiota's influence on brain function is mediated through metabolic processing of certain dietary compounds such as polyphenols [15–18] and synthetic drugs [19–22] by the resident bacteria. Studies from our group and others suggest that the polyphenol metabolites produced by the microbiota modulate immune-inflammatory cascades [23–29], synaptic maladaptation [30–32], mood disorders [33, 34] as well as age-related neurodegenerative disorders [18, 31, 32, 35]. Given this ability of the microbiota to generate unique bioactive compounds, efforts have been made to manipulate the gut microbiota to improve the delivery and efficacy of orally consumed compounds, including phyto-drugs [36–38]. However, the role gut microbiota has on polyphenol metabolism remains elusive. Further efforts should explore how specific members of the gut microbiota promote polyphenol biotransformation in order to develop novel therapeutic strategies through probiotic bacteria.

WHAT IS THE GUT MICROBIOTA?

The gut microbiota is a community of diverse bacteria and microorganisms that form symbiotic relationships with their hosts to maintain host health [39, 40] The influence of the gut microbiota on the host is so complex that the gut microbiota is now considered to be an independent endocrine organ [41] with vast metabolic activities and the capacity to modulate several physiological states including inflammation, oxidative stress [42], and as this review will focus on, neurological processes [43]. The significant impact of the gut microbiota on host metabolism was amply illustrated when transplantaion of gut bacteria from twins discordant for obesity into mice resulted in identical metabolic phenotypes of the microbiota donor [44]. The compositon of the gut microbiota varies significantly between healthy individuals due to diet, antibiotic usage, exposure to pharmaceutical agents, interactions with the environment, physiological and psychological stress [45,46]. Although hundreds of various microbe families have been found in the GI tract [47], each individual harbors a unique combination of these microbes [48, 49]. Despite this diversity, a standard healthy gut microbiota profile has emerged as the composition of the microbiota is now recognized as an important factor in understanding individual nutritional needs [50,51]. Recent research has shown that a healthy gut microbiota is composed of a high proportion of metabolically-active butyrate-producing bacteria including the *Ruminococcus* spp. and *Eubacterium* spp., *Bifidobacterium* spp., which degrade long chain dietary fibers, a low ratio of the principle phyla Firmicutes to Bacteriodetes, and a reduced proportion of inflammatory pathogens including the Proteobacteria [52–54]. As a more accurate profile of the gut microbiota develops, efforts will look at the metabolic activity of specific bacteria and their role in generating biologically active compounds, such as compounds derived from dietary polyphenols

THE GUT MICROBIOTA AND ITS ROLE IN THE GENERATION OF BIOACTIVE POLYPHENOLIC METABOLITES

Research to date on the relationship between polyphenols and bacteria in the GI tract indicate that gut bacteria possess innate mechanisms that generate de novo and potentially bioactive compounds when provided with dietary polyphenols (Fig. 1). The gut microbiota is critical to enabling the bioavailability of ingested polyphenols as most parent polyphenols are not well absorbed by the small intestine [55]. Likewise, 90% of ingested polyphenols reach the large intestine and within the context of the resident microbiota, are transformed into bioavailable products. Following the ingestion of polyphenol compounds, usually in their glycosylated form, bacteria in the GI tract convert dietary polyphenols to low-molecular-weight phenolic compounds, such as phenolic acids [56, 57], that can be more efficiently absorbed by intestinal epithelial cells [58, 59] In some cases, biotransformation by the gut microbiota is essential to providing bioavailable polyphenolic acids. Polyphenols have been shown to undergo a variety of enzymatic processes by bacterial populations in the GI tract. These include the hydrolysis of glycosylaed flavonoids, acylation of flavanol-3-ols ad esterification of hydroxycinnamic acids [60]. Subsequent to enzymatic processing by bacteria, the polyphenol derivatives, usually the aglycons or hydroxyphenylacetic acids, are absorbed by epithelial cells of the small intestine. Once the polyphenol derivatives are in a form capable of being absorbed by the small intestine or colon, they undergo enterocyte phase II modifications, in which they are often converted to their O-Glucuronide or O-Sulfonate forms through methylation, sulfation, hydroxylation, and glucoronidation. Multimeric polyphenols that are not broken down in the small intestine move through the GI tract where their conjugating moieties are processed by colon specific bacteria and absorbed into the epithelial tissue for phase II metabolism [61] The modified polyphenols, from the enterocytes, then enter the blood Stream via the portal vein, are delivered to the liver where they can be further modified via conjugations, and finally are either secreted as bile components back into the intestine for enterohepatic recirculation, or into the blood stream to be delivered to the peripheral tissues including the brain [60].

One recent study demonstrated how a polyphenol-rich potato extract containing cholorogenic, caffeic, and ferulic acids was broken down in a colonic simulator containing human gut microbiota into several biotransformation products. A small proportion of the metabolites were transduced across a Caco-2/HepG2 co-culture; however, the absorption of the secondary metabolites following hepatic transformation resulted in significant increases of ferulic, dihydrocaffeic, 2-hydroxyphenylacetic acid, 3-hydroxyphenylpropionic acid, and coumaric acid [62]. In another study, a simulated gastrointestinal environment composed of rat gut microbiota metabolized three main anthocyanins from mulberry including cyanidin-3-glucoside, cyanidin-3-rutin, and delphinidin-3-rutinoside. Cyanidin-3-glucoside and cyaniding-3-ruitin resulted in protocatechuic, vanillic, and p-coumeric acids while deiphinidin-3-rutinoside into gallic acid, syringic acid, and 2,4,6-trihydroxybenzaldehyde: processes that were dependent on the presence of the gut microbiota [63]. In a cohort of elderly Japanese individuals, the composition of the gut microbiota was highly correlated with the rate of quercetin metabolism. The abundance of Surreellaceae and Oscillospiraceae were negatively correlated with quercetin metabolism, while Fusobacteria and

Enterobacteriaceae showed a positive correlation [64], Furthermore, using 20 healthy volunteers who were administered green tea, one study found that colonic microbiota produced polyhydroxyphenyl-γ-valerolactones, which was the urinary catabolite produced in the greatest concentrations; it was shown to have a 10 times greater concentration than the other flavan-3-ol conjugates [65]. Recently phenyl-γ-valerolactones have been purported to provide protection to brown adipocytes against oxidative damage, which may provide an important observation for research into obesity [66].

Our group has shown that mice administered with grape seed polyphenol extract (GSPE) resulted in the production of 11 unique polyphenol metabolites, as measured in urine, and 4 as measured in the plasma, while only of the 2 metabolites, 3-HBA and 3-HPP, were detected in the brain following perfusion (Fig. 2, adapted from Wang et al. [35]), Both 3-HBA and 3-HPP are likely derivatives of the flavonol quercetin and are produced following ring scission by *Enterobacteria* spp. in the gut and subsequent enterocyte phase II modification such as dehydration or reduction [67]. Another study using dietary supplementation with a red wine polyphenolic extract found that the addition of *Lactobacillus plantarum* increased the conversion of monomeric flavanols, such as those found in GSPE, and their intermediate metabolites into phenylpropionic acids, in particular 3-(3′-hydroxyphenyl) propionic acid (3-HPPA) [68]. *In vivo* studies using germ-free or antibiotic-treated mice also support the necessity of gut microbes for the conversion of polyphenol compounds into bioactive and bioavailable compounds whose concentration without bacteria metabolism would be subclinical 18, 68–72].

THE IDENTIFICATION OF BACTERIA CAPABLE OF CONVERTING POLYPHENOLS INTO BIOACTIVE COMPOUNDS

To best understand the role of gut bacteria in the breakdown of polyphenols into bioactive metabolites, it is critical to determine specific bacterial strains responsible for the enzymatic processing of polyphenols Understanding the catalytic abilites of each bacterial species will provide an opportunity to bio-engineer next-generation probiotics that most effectively transform polyphenols into the desired bioactive metabolites.

Several enzymes necessary for the biotransformation of dietary polyphenols have been identified. *Eubacterium ramulus* induces ring fission of the polyphenolic core generating several metabolites with altered health benefits [73]. For example, degradation of naringen by calchone isomerase and phloretin hydrolase converts the complex polyphenol into usable aromatic products [74] From the green tea polyphenols catechins, epicatechin, epicatechin galate, and epigallocatechin galate, 4-hydrobeenzoic acid and vanillic acid are produced [75] For example, ferulic acid, a hydroxycinnamic acid found in plant stems and various herbs, is broken down by the esterase activity of Lactobacillus spp. into 4-vinylguaiacol and hydroferulic acid [76]. Further breakdown converts these products into the caffeic and vanillic acid, which have potent therapeutic effects especially in Alzheimer's disease (AD) [77]. Soya-ioflavone daidzein is converted exclusively in equol only by *Adlercreutiza equolifaciens,* giving it a greater pro-estrogenic effect [78] Furthermore, the conversion of ellagic acid into urolithin is conducted by *Gordonibacter urolithinfaciens;* however the

accumulation of the variety of biotransformaion products was dependent on the presence of the complex microbiota [79]. Another important biotransformation elicited by the gut microbiota, notably *Flavonifractor plautii,* is the conversion proanthocyanidins into 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone (DHPV) [60, 80]. This is an important conversion as the anti-inflammatory action of DHPV is greater than its parent metabolites, notably the TNF-α-mediated induction of proinflammatory factors from monocytes. In addition to these examples, several other metabolites of gut bacterial biotransformation in the GI tract are outlined in a comprehensive review by Rowland et al. [81].

Despite the large body of evidence supporting the role of the gut bacteria and their specific enzymes in the biotransformation of polyphenols, understanding the breadth of the microbiota's effect on polyphenol metabolism remains in its infancy. Likewise, novel approaches are necessary in order to elucidate the specific activities of select bacteria and their role in polyphenolic biotransformation. A recent approach to characterize gut bacterial populations leveraged a method of metagenomic binning of bacterial DNA methylation to create bacterial barcodes for efficient identification of unique bacterial strains [82]. Other groups including ours, have used gnotobiotic and germ-free mice to manipulate bacterial populations to better understand host metabolism. With these new methods, we will be able to clarify the unique metabolism of gut microbiota, which differs between individuals, and how this may determine the bioavailbility and bioactivities of polyphenol metabolites [83, 84]

HUMANIZED GNOTOBIOTIC MICE AS A MODEL SYSTEM TO EXPLORE THE RELATIONSHIP BETWEEN THE HUMAN GUT MICROBIOTA AND THE BIOAVAILABILITY OF DIETARY POLYPHENOL PREPARATIONS

Mice raised in germ-free environments provide an excellent system for understanding the role of gut bacteria in various aspects of host physiology. Germ-free mice can be colonized at specific life stages with a complex or defined consortia of microbes to understand the role of the gut microbiota in host physiology using a highly controlled and easily manipulated system. One germ free mouse model found that consistent with *in vitro* evidence supporting the relevance of gut microbiota in the bioconversion and bioavailability of phenolic metabolites from botanical polyphenol components [85–87], germ-free mice or antibiotic-treated mice had decreased bioconversion of orally consumed polyphenol compounds to phenolic acid within their intestinal tract [88]. We recently developed and validated other methods for the transplantation of the human gut microbiota into gnotobiotic animals [89]. These humanized gnotobiotic mice have a high engraftment rate with 88% of genus-level taxa from the donor detected in the mice, while the genera that did not engraft were at very low abundance in the donor sample (0.008% on average). The applicability of these models to study human disease was evident when mice humanized with the microbiota of twins discordant for obesity developed phenotypes seen in the human host. Specifically, mice transplanted with gut microbiota of an obese twin had a higher increase in fat mass than mice transplanted with the corresponding lean twin microbiota [44]. The implications of these inter-individual variabilities on gut microbes and how they may influence the bioconversion of polyphenols in bioactive metabolites are further discussed below.

To the author's knowledge, there are currently no published studies that directly explore the relationship between the human gut microbiota and the diversity and abundance of bioactive phenolic metabolites *in vivo.* Therefore, we currently are pursuing studies to characterize germ-free mice models to understand polyphenol metabolism. The microbiota of different human donors can be transplanted into separate groups of gnotobiotic mice to estimate variation in bioavailability of bioactive botanical polyphenols as a function of donor microbiota (Fig. 3A). High-throughput bacterial isolation can then be used to isolate a large proportion of the gut microbes from two donors of interest into personalized arrayed culture collections (one donor is shown) (Fig. 3B). These personal culture collections can be screened using a combinatorial gnotobiotic approach combined with statistical modeling to identify specific microbial strains that modulate the bioactive compounds of interest (target metabolites will be based on our prior research) (Fig. 3C). We believe our studies complement transplantation of human microbiota to gnotobiotic mice [84, 90]. With advancing genomic technologies allowing researchers to isolate, archive, and retrieve a large number of gut bacteria [48, 91], the necessary tools to identify and use a combination of gnotobiotic mice to possibly identify the microbial strains that modulate the metabolisin of bioactive polyphenols in the serum and the brain are now available [92].

EMERGING EVIDENCE FOR THE ROLE OF THE GUT MICROBIOTA IN MOOD DISORDERS

The gut-brain axis (GBA) is a dynamic bidirectional system that is composed of the intestinal microbiota, the enteric nervous system, the peripheral and central nervous systems, humoral pathways, cytokines, neuropeptides and other signaling molecules [93]. The gut microbiota is critical not only for the production of polyphenol metabolites but also for functionality of the GBA and ultimately, neurological functions. The GI tract communicates with the brain through neuronal afferents, such as the vagus nerve, endocrine messages carried by the gut hormones and metabolic signaling, and immunological messages with cytokines [94]. With the emergence of evidence supporting a bi-directional relationship between the gut microbiota and the brain, the scientific community has begun to implicate the gut microbiota as a mediator of cognitive health [95]. The 2009 Walkerton Health Study that assessed participants with irritable bowel syndrome (IBS) over an eight-year period found that depression and anxiety were important risk factors for the persistence of IBS symptoms [96]. Studies such as the Walkerton Study, which revealed associations between gut microbes and the brain provoked an imperative to determine if psychiatric symptoms can be driven by gut dysbiosis [97–100]. One study supported this notion by showing that germ-free mice exhibited reduced anxious behavior as compared to specific pathogen free mice [101]. In spite of recent efforts and observations into a relationship between gut bacteria and mood disorders, explicit evidence indicating a mechanism of bidirectional communication between the gut and neuropsychiatric disorders remains elusive.

POLYPHENOLS: POTENTIAL THERAPEUTIC APPLICATIONS IN NEUROLOGICAL DISORDERS

Given the influence the gut-brain axis may have on the etiology of mood and behavioral disorders, our group set out to understand the capacity to which polyphenol metabolites produced by the gut microbiota can attenuate underlying physiological mechanisms of neurological disorders. Gut processed dietary polyphenols are plant-derived micronutrients found in high concentrations in certain diets such as the Mediterranean diet [86–88]. These compounds are associated with an array of health benefits and are a potential means to prevent a number of diseases [102–108]. Recent work from our group found that several polyphenol metabolites from grape seed extract (GSPE), concord grape juice (CGJ) and resveratrol (RSV), were able to protect against neuropathology and cognitive impairment in neurodegenerative disorders such as AD [35, 102, 103, 109–112] and related tau-mediated neurodegenerative disorders [113–116]. These studies led to the identification of 26 polyphenol metabolites from GSPE, CGJ, and RSV and each were found to accumulate in blood, and a subset in the brain, which had potential to modulate biological activitis *in vivo* [30, 31, 117–120] Moreover we found polyphenol metabolites that were present in the brain such as 3′-O-Me-epicatechin-5-glucuronide [32] and quercetin glucuronide [31]. 3-hydroxybenzoic acid and 3-(3′-hydroxyphenyl) propionic acid were primarily responsible for inhibiting the onset and progression of AD-type pathophysiology [18]. The compounds exerted their nuroprotective effects by interfering with the generation of neurotoxic AD-type amyloid-β peptides, which can interfere with neuroplasticity and memory consolidation. In addition to interfering with AD mechanisms, studies demonstrated that multiple biologically available microbiota-derived phenolic acids including 3,4-dihydroxypenylacetic acid, 3-(3′-hydroxyphenyl) propionic acid, 3,4-dihydroxyhydrocinnamic acid and homovanillic acid from a bioactive dietary polyphenol preparation (BDPP), composed of GSPR, CGJ, and RSV, were able to modulate biological mechanisms associated with inflammation and synaptic plasticity [18, 30, 121]. These processes are known to influence psychological and cognitive resilience in, for example, animal models of social defeat and sleep deprivation. The collective evidence from our group and from other investigators [83, 122–129] implicates gut-derived biologically available phenolic metabolites as primary facilitators of the observed health benefits associated with polyphenol rich diets.

Depression and depression-like disorder are major contributors to the expanding health costs in the United States [100]. The treatment options currently available, which target neurochemical or neurobiological mechanisms identified retrospectively following discovery of the drug's initial antidepressant efficacy, produce temporary remission for approximately 50% of patients [99,100,130]. Such discouraging evidence highlights the need for novel therapeutics that can target genetic or proteomic mechanisms underlying depression. Accumulating evidence suggests that immunological abnormalities, particularly imbalances in select pro-inflammatory mediators, play important roles in the expression and continuity of depressive symptoms in vulnerable individuals [131]. These inflammatory mediators are now recognized as important biological signatures as well as key mechanistic contributory factors of depression. As such, these inflammatory mediators are also considered important novel therapeutic targets for depression [132].

Polyphenols can potentially modulate depressive disorders through their potent anti-inflammatory effects [133–139]. It has been suggested that polyphenols attenuate inflammatory conditions via its inherent anti-oxidative [134] capabilities; oxidative stress directly facilities the production of numerous proinflammatory cytokines and has been shown to contribute to the progression of cancer [140]. Futhermore, oxidative stress can either directly decrease neuronal plasticity through covalent interactions with protein involved in axonal transport or synaptic integrity, which results in synaptic degeneration and neuronal apoptosis or indirectly through the aforementioned production of cytokines [141]. This preclinical evidence gave encouragement to our group that the administration of select bioactive polyphenol-rich preparation may intercede with the deleterious mechanisms of radical oxygen species and could attenuate depressive phenotypes in clinical conditions that often persist in spite of treatment with a serotonin selective reuptake inhibitor, such as major depressive disorder provoked anhedonia, characterized by a markedly diminished response to pleasure [131–133, 142–144] that is linked to impaired psychosocial functioning, poor treatment outcome, and suicidal behavior. Moreover, the current evidence emphasized in the review supports the potential therapeutic application of a combination of polyphenols, such as BDPP, largely reported by our group, in promoting resilience against the underlying heightened inflammatory mechanisms in stress induced depression [145]. As we expand our preclinical studies, we will look in to whether it is warranted to support further clinical development of BDPP for treating depression.

CONCLUSION

Of the numerous ways symbiotic bacteria in the GI tract influence homeostasis and affect the health of its host, a novel perspective looks at their ability to supply their host with bioactive and bioavailable compounds. As polyphenols have been shown to promote cognitive resilience against a variety of neurological disorders, work from our group, as well as others, has shown that these effects are mediated through microbiota metabolism and the subsequent generation of bioactive and bioavailable polyphenol metabolites. Further investigations should expand into understanding the specific bacteria responsible for the generation of these polyphenol metabolites. As summarized in Fig. 4, one could conjecture a strategy to develop next generation probiotic therapeutics that supplement bacteria known to promote psychological and cognitive resilience via its generation of bioactive compounds.

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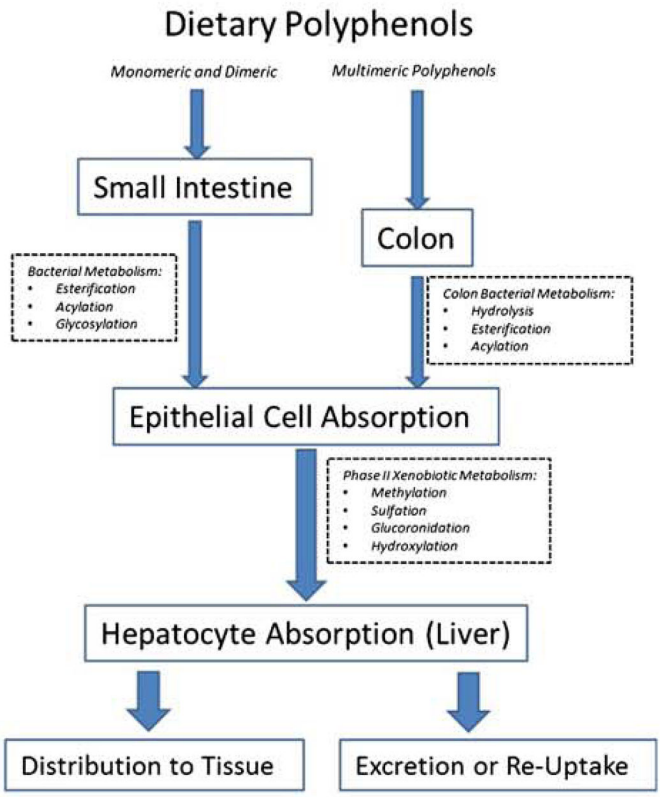

Fig. 1.

The diversity of interpersonal bacteria differentially metabolizes polyphenols. After oral consumption, monomeric polyphenols undergo a variety of covalent modifications, such as acylation or esterfication, catalyzed by the bacterial enzymes unique to the upper gastrointestinal tract. The modified polyphenols then transit into the epithethial cells of the upper GI tract where they undergo enterocyte modifications by phase II metabolisim that involves the conjugation of glucuronide, methyl or hydroxyl groups. Multimeric polyphenol compounds pass through the small intestine because the resident bacteria do no transcribe hydrolytic enzymes required for the production of monomeric polyphenols, and their molecular weight prevents their uptake into upper GI epithethial cells. They pass into the colon where resident bacteria hydrolyze conjugating moieties of multimeric polyphenols allowing for their absorption and metabolic processing into simple phenols by colon epithelial cells. Another set of covalent modifications can occur when polyphenol metabolites pass through the portal vein and reach liver hepatocytes, whereupon they undergo additional phase II modifications. The polyphenol derivatives are then either distributed to the target tissue by circulation, or are excreted as bile for enterohepatic circulation or excretion. The interpersonal diversity of microbiota, represented in the scheme by the red bacteria, can substantially alter the potential bioavailability and bioactivity of a polyphenol's derivatives, and subsequently their therapeutic efficacy in models of induced cognitive dysfunction.

A

Metabolite	Urine *(nmol/day)*	Plasma *(μM)*	Brain *(μM)*
3-HBA	9.2	(-)	1.75
3-HPA	1	(-)	(-)
3-HPP	627.3	0.92	2.53
3-HHA	54.8	(-)	(-)
34-HBA	366.2	(-)	(-)
4-HHA	241.5	(-)	(-)
5-HPV	78.7	0.48	(-)
3,4-diHPA	2.5	(-)	(-)
3,4-diHPP	590.5	1.25	(-)
HA	22.2	4.72	(-)
FA	128.2	(-)	(-)

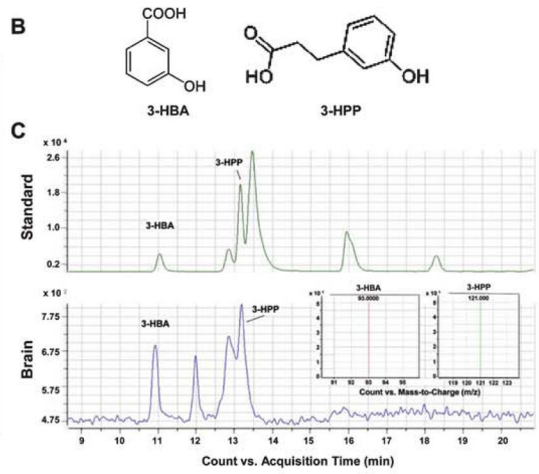

Fig. 2.

Polyphenol metabolites measured in urine, plasma and in the brain following the administration of GSPE. A) The administration of GSPE, at 250 mg/BW, to Sprague Dawley rats by gavage for 10 days resulted in the identification of eleven unique phenolic acids the urine, four of which were also found in the plasma, and two in the brain. B) Of the two quantified phenolic acids in the brain, 3-(3′-hydroxyphenyl) propionic acid (3-HPP) is a known derivative of the flavonol quercetin, the flavone apigenin, and of the flavan-3-ols catechin or epicatechin, which are processed by respective bacteria *Enterococcus casseliflavus, Clostridium coccoides,* and *C. orbiscindens* [60]. Meanwhile, the second brain quantified phenolic acid, 3-hydroxybenzoic acid (3-HBA), is known to be a derivative of the anthocyanin, cyanidin, which undergoes enzymatic processing by either *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, or Bifidobacterium lactis* [60]. C) The concentration of each phenolic acid was determined via LC-MS/MS, using analytical grade molecular standards (top) and a sample brain specimen (top).

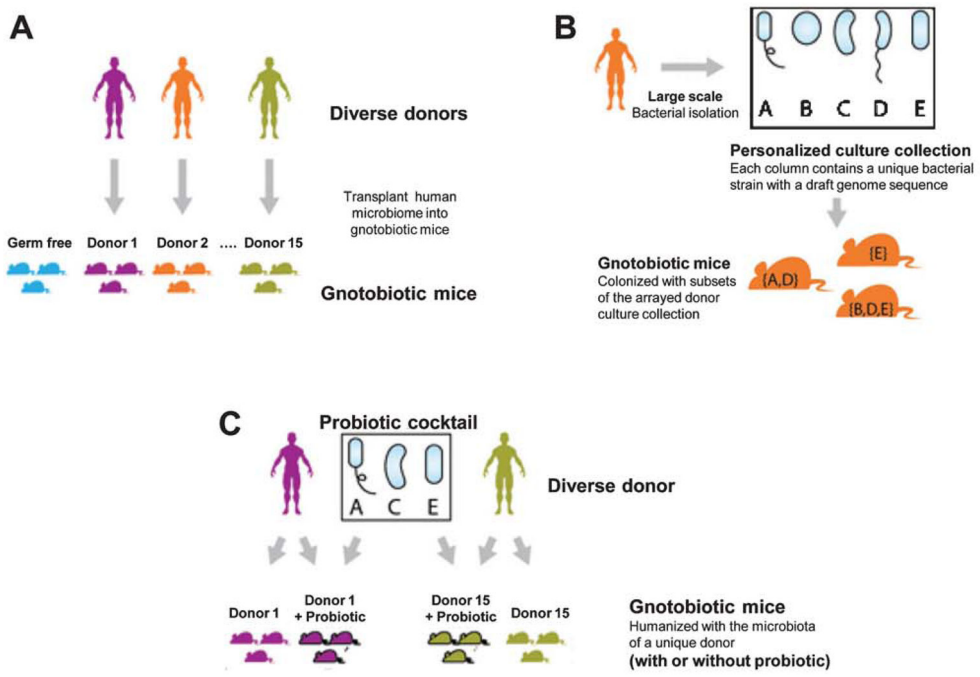

Fig. 3.

The strategy used to identify interpersonal differences in the composition of the human GI microbiota. In order to understand the role individual bacteria play in the generation of polyphenol metabolites, a strategy was developed whereby (A) bacteria from a human gastrointestinal tract was transplanted to one of a gnotobiotic mouse; (B) the transplanted bacteria were analyzed through statistical methods to isolate unique strains and then transplanted into mice; (C) bacteria that were identified to produce specific metabolites were isolated, expanded, and transplanted into gnotobiotic mice to serve as a model system for next generation probiotics.

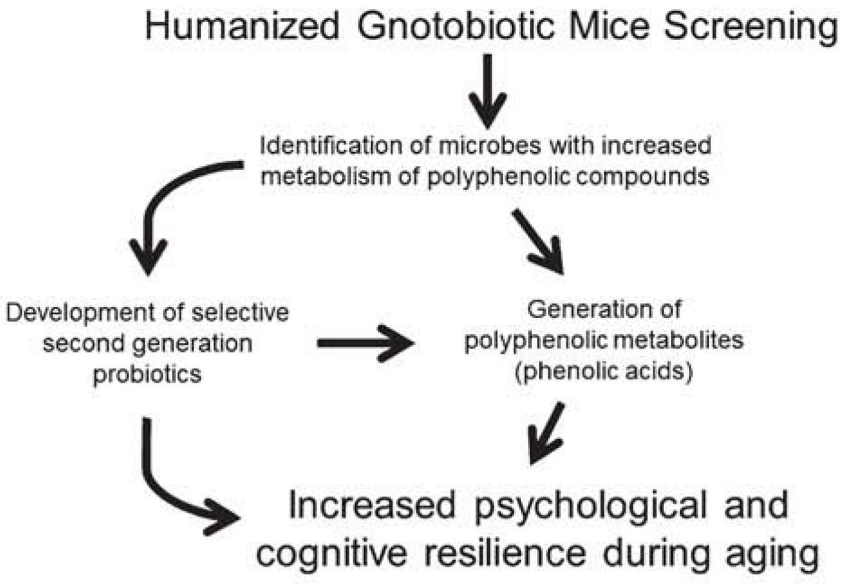

Fig. 4.

Development strategy for the generation of bioactive polyphenol metabolites using probiotics. As the metabolism of polyphenols by the microbiome becomes clearer it will be possible to identify the unique bacterial populations responsible for the generation of bioactive polyphenols. Gnotobiotic mice constitute an important tool to achieve this goal; they will allow future research groups the ability to selective transplant bacterial strains into the gastrointestinal tract and to determine their unique metabolic function on polyphenols. Ultimately, the goal will be to develop therapeutic approaches to increase the bioavailability of polyphenol derivatives that have properties capable of promoting resilience against age or stress induced cognitive dysfunction, and its potential mediator inflammation.