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MASI: microbiota—active substance interactions database

Xian Zeng[1], Xue Yang[1], Jiajun Fan[1], Ying Tan[2], Lingyi Ju[1], Wanxiang Shen[3], Yali Wang[3], Xinghao Wang[2], Weiping Chen[4,*], Dianwen Ju[1,*] and Yu Zong Chen[3,*]

[1]Department of Biological Medicines & Shanghai Engineering Research Center of Immunotherapeutics, Fudan University School of Pharmacy, Shanghai 201203, P. R. China, [2]The State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Biology, Tsinghua University Shenzhen Graduate School, Shenzhen Technology and Engineering Laboratory for Personalized Cancer Diagnostics and Therapeutics, Shenzhen Kivita Innovative Drug Discovery Institute, Guangdong, P. R. China, [3]Bioinformatics and Drug Design group, Department of Pharmacy, National University of Singapore, Singapore 117543, Singapore and [4]Key Lab of Agricultural Products Processing and Quality Control of Nanchang City, Jiangxi Agricultural University, Nanchang, 330045, P. R. China

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ABSTRACT

Xenobiotic and host active substances interact with gut microbiota to influence human health and therapeutics. Dietary, pharmaceutical, herbal and environmental substances are modified by microbiota with altered bioavailabilities, bioactivities and toxic effects. Xenobiotics also affect microbiota with health implications. Knowledge of these microbiota and active substance interactions is important for understanding microbiota-regulated functions and therapeutics. Established microbiota databases provide useful information about the microbiota-disease associations, diet and drug interventions, and microbiota modulation of drugs. However, there is insufficient information on the active substances modified by microbiota and the abundance of gut bacteria in humans. Only ∼7% drugs are covered by the established databases. To complement these databases, we developed MASI, Microbiota—Active Substance Interactions database, for providing the information about the microbiota alteration of various substances, substance alteration of microbiota, and the abundance of gut bacteria in humans. These include 1,051 pharmaceutical, 103 dietary, 119 herbal, 46 probiotic, 142 environmental substances interacting with 806 microbiota species linked to 56 diseases and 784 microbiota–disease associations. MASI covers 11 215 bacteria-pharmaceutical, 914 bacteria-herbal, 309 bacteria-dietary, 753 bacteria-environmental substance interactions and the abundance profiles of 259 bacteria species in 3465 patients and 5334 healthy individuals. MASI is freely accessible at http://www.aiddlab.com/MASI.

INTRODUCTION

The interactions of xenobiotic and host active substances with gut microbiota play key roles in human health, diseases and physiological responsiveness to various cues and treatments (1–3). Broad variety of xenobiotics such as dietary components (4), pharmaceuticals (2,5,6), herbal products (7) and environmental chemicals (8,9) are modified by microbiota with altered bioavailabilities, bioactivities and toxic effects in the host. Some of these xenobiotics can also alter microbiota to affect their functions and communications with the host (8,10). Probiotics have been used for altering the composition of the gut microbiome and introducing beneficial effects to gut microbial communities (11). The comprehensive knowledge of the interaction of microbiota with the diverse active substances is important for understanding microbiota function and for developing improved therapeutics (12–15).

Several microbiota databases have been developed for facilitating the research of the microbiota and its interactions with active substances. PharmacoMicrobiomic gives the information of microbiota regulation of drugs (covers 24 gut bacteria and 106 drugs) (16). Disbiome presents 10 684 microbiota–disease associations in a standardized way (17). Virtual Metabolic Human database (VMH) contains 17,730 unique reactions of microbiome metabolism with nutrition and diseases (18). gutMDisorder provides 2263/930 associations between 579/273 gut bacteria and 123/33 disorders or 77/151 interventions in human/mouse (19). These

*To whom correspondence should be addressed. Tel: +65 6516 6877; Fax: +65 6774 6756; Email: phacyz@nus.edu.sg
Correspondence may also be addressed to Dianwen Ju. Tel: +86 51980037; Fax: +86 51980037; Email: dianwenju@fudan.edu.cn
Correspondence may also be addressed to Weiping Chen. Tel: +86 791 8381 3420; Fax: +86 791 8381 3655; Email: iaochen@163.com

databases provide useful information about the microbiota-disease associations, diet and drug intervention of microbiota, and microbiota modulation of drugs. However, there is insufficient or lack of information about microbiota modification of drugs, dietary components, herbal products, and environmental chemicals. Only 152 of the > 2000 approved drugs are covered by these databases. Moreover, in these databases, no data is provided for the relative abundance of microbial species in human microbiota samples.

Therefore, expanded resources are needed for the information of more variety of microbiota and active substance interactions, and the relative abundance data of microbial species. To complement established databases for the additional information, we developed a new database MASI, Microbiota—Active Substance Interactions, to provide the information of microbiota alteration of active substances and active substance alteration of microbiota. The active substances include comprehensive sets of therapeutic drugs, diets/dietary components, herbal substances, probiotic products, and environmental chemicals modulated by the microbiota species or involved in the regulation of the microbiota species. Convenient search facilities were set up for keyword search and for browsing by individual classes of drugs, bacteria-active substance interactions (drug, diet, herbal substance, probiotics, environmental chemical) and bacteria–disease associations.

DATA COLLECTION AND PROCESSING

The information of microbiota alteration of active substances and active substance alteration of microbiota were searched from the literature database PubMed (20), by using the combinations of keywords 'microbiota', 'microbiome', 'microbe', 'bacteria', 'gut', 'intestinal', 'xenobiotics', 'chemical', 'metabolite', 'metabolism', 'biotransformation', 'modulating', 'modulation', 'regulating', 'regulation', 'restoring', 'restoration', 'drug', 'therapeutic', 'food', 'dietary', 'nutrient', 'nutraceutical', 'probiotics', 'probiotic', 'prebiotics', 'herb', 'herbal', 'medicine', 'extract', 'environmental' and 'environment'. Only the experimentally determined interactions, modulations, or regulations were included in MASI. The literature-reported interaction records were manually extracted from the individual publications. The experimental details (e.g. experimental condition, chemical exposure dose and duration, effects on the host) of bacteria and active substance interactions reported in original publications were also collected when available. These interaction records were categorized into two classes, the bacteria and active substance interactions, and the bacteria and dietary substance interactions.

For the identified bacteria species, their taxonomic information down to genus level was extracted from the NCBI taxonomy database (21). The active substances include drugs, herbs, traditional medicines, environmental chemicals/pollutants and other bioactive compounds. The bacteria and active substance interactions are further divided into the subclasses of bacteria alteration of active substances and active substance alteration of bacteria. The bacteria and dietary substance interactions are currently of a single type, i.e., dietary substance alteration of bacteria. In order for convenient access of the bacteria–disease associations relevant to the collected bacteria and active substance interactions, we further searched PubMed for the relevant bacteria-disease associations using the name of each collected bacteria and the keywords 'disease', 'disorder', 'syndrome', 'cancer', 'leukemia', 'infection', 'inflammation', 'inflammatory', 'allergy', 'asthma', 'arthritis', 'diabetes', 'obesity', 'fibrosis', 'cirrhosis', 'Parkinson's', 'epilepsy', 'sepsis', 'colitis', 'fatigue', 'constipation', 'enterocolitis' and 'eczema'. The searched literatures were manually evaluated for finding the experimentally indicated bacteria-disease relationship, i.e. the increase/decrease of the relative abundance of the bacteria is associated with the disease. Moreover, probiotics were extracted from Probio database (22) by the bacteria species matching using the corresponding scientific name or NCBI taxonomic identifier.

The SMILES strings of the chemical substances were extracted from PubChem database (23) by matching PubChem CID identifiers or by manual matching and inspection of the substance names with those in the PubChem records. The SMILES strings were subsequently converted to structure images using OpenBabel command line script (24). The Anatomical Therapeutic Chemical Classification System (ATC) codes of the drugs were from DrugBank database (25) by matching DrugBank identifiers or PubChem CID identifiers with those in the DrugBank records. Cytoscape software (26) was used for generating the bacteria-substance-disease association networks, which are provided in the respective MASI webpage for visualization.

The pre-processed gut bacteria abundance level in the patients and healthy individuals are from the curatedMetagenomicData resource (27). The curatedMetagenomicData processes metagenomic data with a unified analysis pipeline to calculate the relative abundance from raw sequencing data. In the relative abundance matrix, the sum of microbial abundance of an individual microbiota sample was standardized to 1 at each taxonomic level (e.g. species, genus, family). Relative abundance of each bacteria species was $\log_{10}$ transformed (resulted relative abundance levels range from –7 to 0) for convenient visualization. Ridgeline plots were generated using ggplot2 R package to show relative abundance profiles of individual bacteria species across ages and geographical regions of patients, and disease conditions.

MICROBIOTA AND ACTIVE SUBSTANCE INTERACTIONS

Active substances such as drugs, dietary supplements, herbal products and probiotics have been widely used for therapeutic, nutritional and health beneficial effects. Many of these active substances affect microbiota with either beneficial or adverse effects. For example, in a study of >1000 approved non-antibiotic drugs against 40 representative gut bacterial strains, there appear to be partially overlapped resistance mechanisms of antibiotics and non-antibiotic drugs, suggesting that microbial species which are multi-drug resistant to antibiotics may in some cases be more resistant to human-targeted drugs (28). Various strategies have been explored for improved therapeutic response in cancer treatment by the modulation of gut mi-

Figure 1. The homepage of MASI web interface. The webpage allows users to search microbiota species, therapeutic substances, or disease by keywords. All entries of MASI can be browsed or downloaded by clicking the 'Browse' or 'Download' buttons in the top menu.

crobiome, which include faecal microbiota transplants, probiotics, diet, and prebiotics intervention (29,30). The consumption of antibiotic drugs may alter the host microbiota, resulting in dysregulation of host immune homeostasis and an increased susceptibility to disease (31,32). The antihyperlipidemic function of *Coptis chinensis* alkaloids partly arise from their modulation of gut microbiota and bile acid pathway to reduce triglycerides, total cholesterols, low-density lipoprotein cholesterols, lipopolysaccharides, and total bile acids, leading to the beneficial effects in the treatment of high-fat diet induced hyperlipidemia (33). Therefore, the information of the regulation of microbiota by active substances is important for the investigations and manipulations of gut microbiota in searching of improved therapeutics.

Moreover, many drugs, dietary components, and herbal products are modified by gut microbiota with functional and therapeutic implications. For instance, the nucleoside analog drug brivudine can be converted to hepatotoxic bromovinyluracil by both mammalian and microbial enzymes, suggesting a microbiome contribution to brivudine pharmacokinetics and toxicity (13). Studies of 271 clinical drugs have found 176 drugs metabolized by at least 1 of the 76 tested human gut bacterial strains, some of which are expected to influence intestinal and systemic drug and drug-metabolite exposure (5). Dietary fibers are metabolized by gut microbiota into short-chain fatty acids, which mediate gut-brain communications with beneficial effects on cognitive, immune and endocrine functions (34). Ellagitannin-rich herbs are popular remedies in the treatment of various inflammatory diseases, and ellagitannins in these herbs are metabolized by gut microbiota into anti-inflammatory urolithins partly responsible for their observed beneficial effects (35). Hence, the knowledge of the modulation of active substances by microbiota is highly useful for the full understanding and exploration of the effects of drugs, foods and herbal products on human health.

MICROBIOTA INTERACTIONS WITH ENVIROMENTAL CHEMICALS

Environmental chemicals strongly influence microbiota communities with implications to human health (8,36). In a study of the impact of confined swine farm environments on gut microbiome and resistome of veterinary students, it has been found that farm exposure shapes the gut microbiome of these students, with enrichment of potentially pathogenic taxa and antimicrobial resistance genes (37). The potentially adverse effects include increased risk of adenocarcinoma in the lower esophagus and decreased modulation of immunologic, endocrine, and physiologic functions in the stomach. The potentially beneficial effects include decreased risks of ulcers, gastric adenocarcinoma and lymphoma. Bisphenol A (BPA), a plastic monomer of high-volume industrial chemical with endocrine-disrupting toxicity, has been found to alter a variety of gut microbiota species (26). For instance, BPA exposure has led to increased *Prevotellaceae* in the gut microbiome of male mice, which may affect the mucosal barrier function (38), BPA exposure has also led to upregulated *Akkermansia* and *Methanobrevibacter* in the gut microbiome of males, which is of concern of cancer risks because *Akkermansia* is involved in butyrate production and is frequently elevated in human cancers (39,40). A third study has found that exposure to trace-level dust from a high biodiversity soil can change gut microbiota in comparison to dust from low biodiversity soil or no soil, which indicates that biodiverse soils may be an important source of butyrate-producing bacteria for resupplying the mammalian gut microbiome with potential gut and mental health benefits (41). Thus, information of the interactions between microbiota and environment is needed for a more complete investigation and understanding of the microbiota functions and interventions.

GUT BACTERIA ABUNDANCE AND HUMAN HEALTH

The alterations of relative abundance of gut bacteria are closely associated with human health and diseases. For instance, differences in the composition and function of gut microbial communities contribute to individual variations in cytokine responses to microbial stimulations in healthy individuals (42). Moreover, in a recent investigation of the contributions of impaired gut microbial community development to childhood undernutrition, a microbiota-directed complementary food has been identified that changes the abundances of targeted microbiota bacteria, resulting in enhanced growth, bone formation, neurodevelopment, and immune function in children with moderate acute malnutrition (43). Treatment of mice with an antibiotic cocktail results in the perturbation of the abundance of specific

Table 1. Overall statistics of MASI database

	No. of entries
Unique bacteria species	806
Unique substances	1350
Unique diseases	56
Unique bacteria species with abundance profile available	259
Unique bacteria–substance interaction pairs	11 752
Unique interaction pairs: bacteria alter substances	4001
Unique interaction pairs: substances alter bacteria abundance	7770
Unique bacteria–disease associations	784

members of the microbiota communities, and the perturbation impairs the response of subcutaneous tumors to CpG-oligonucleotide immunotherapy and platinum chemotherapy (44). Therefore, gut bacteria abundance information is essential for the investigation of the microbiota and its interaction with active substance.

DATABASE CONTENTS, STRUCTURE, AND ACCESS

MASI is freely accessible at http://www.aiddlab.com/MASI (homepage in Figure 1). As shown in Table 1, it currently covers 11 215 bacteria-drug, 914 bacteria-herbal substance, 309 bacteria-dietary component, 753 bacteria-environmental chemical interactions. These interactions involve 980 approved drugs, 103 dietary components, 119 herbal substances, 46 probiotic products and 142 environmental chemicals interacting with 806 bacteria species and in 56 human diseases. The relative abundance profiles of 259 bacteria species in 3465 patients and 5334 healthy individuals are provided. Among four substance categories, microbiota-therapeutic substances interactions account for the majority of the total 11 752 interaction records in MASI (Table 2). MASI can be searched by keywords and by browsing the substances (drug, dietary, herbal substance, probiotics, environmental), interactions (microbiota alteration of substance, substance alteration of microbiota), and bacteria-disease associations. In the MASI browse page, the interactions can be filtered by selecting the respective fields of bacteria and active substance interactions, bacteria and dietary substance interactions, bacteria and environmental chemical interactions, and bacteria-disease associations.

For each individual bacteria species, the interaction information was presented in five sections (Figure 2): Section-1 'Bacteria–Drug Interactions' shows the detailed information of alteration effect of bacteria on the bioavailability, bioactivity or toxicity of drugs and alteration effects of drugs on bacteria abundance in human gut or proliferation in *in vitro* assays. Similar information was presented in Section-2 'Bacteria–Herbal Substance Interactions' and Section-3 'Bacteria–Dietary Substance Interactions'. Section-4 shows the 'Bacteria–Disease Associations' to cover those bacteria that have bacteria–active substance interaction records in MASI. Section-5 provides relative abundance profile of the bacteria species in healthy population and various disease conditions. For each individual substance, a substance page provides 'Bacteria–Drug Interactions' and 'Probiotics-Substance Interactions' records relevant to this substance.

As shown in Figure 3, active substances in MASI interaction records tend to concentrate on a few regions on the phylogenetic tree of microbiota species. The number of substances interacting with individual bacteria species ranges from 1 to 203. The top five bacteria species *Roseburia intestinalis, Eubacterium rectale, Bacteroides vulgatus, Clostridium perfringens* and *Coprococcus comes* have 203, 198, 194, 182 and 180 known interactive substances, respectively, while about 83% of bacteria species in MASI have <10 known interactive substances. From higher taxonomic level perspectives, bacteria-active substance interactions mainly distributed in *Bacteroidales* order, *Lachnospiraceae* family and *Escherichia* genus.

MASI was developed with MySQL backend and PHP server software. Its web-interfaces were built with HTML5, PHP, and JavaScript, and were designed to enable the convenient access of its entries by browsing or searching microbiota species, substances (e.g. approved drugs, dietary compounds, medicinal herbs, antibiotics), and diseases. While applicable, the microbiota species entries are cross-linked to NCBI Taxonomy database (21), chemical substances entries are crosslinked to ChEMBL (45), DrugBank (25), Therapeutic Target Database (TTD) (46), PubChem (23) and Natural Product Activity and Species Source database (NPASS) (47). The references for each microbiota-active substance interaction are listed with PubMed identifiers or DOIs below each entry for conveniently tracing back to original studies. All interaction entries can be freely and conveniently downloaded using the download functions provided in each individual bacteria/substance webpage. Alternatively, users can download whole datasets of MASI from the 'Download' webpage with a format of either plain text or Excel tables.

PERSPECTIVES

Microbiota plays vital roles in human health (1) and its malfunction and dysregulation may lead to health problems (37). The state of microbiota and its broad effects is significantly influenced by the interactions of microbiota with various active substances (5,28,35) and environmental chemicals (41). MASI as well as other established microbiota databases (16–19) collectively serve as useful resources for the relevant information and for facilitating the research and exploration of microbiota in the promotion of human health. There have been new advances in the large-scale genomic studies of the functional microbiome of >6000 gut bacteria (48), longitudinal analysis of the ecological states in gut microbiome (49), the mapping of the human microbiome drug metabolizing genes (5), and the design of microbiota-targeted foods for the treatment of diseases promoted by the malfunctional or dysregulated microbiota (43). The rich information generated from these and future investigations can be incorporated into MASI and other established microbiota databases for better serving the microbiota research and exploration efforts. We aim to regularly update the newly-emerging information into MASI.

Table 2. Number of entries of microbiota - active substances interactions in each category/subcategory of substances. One substance may belong to multiple subcategories

Substance category—subcategory	No. of substances	No. of interactions (bacteria alter substances)	No. of interactions (substances alter bacteria abundance)	Total no. of interactions
Therapeutic substance (all)	1074	4134	7081	11 215
Therapeutic substance—approved drug (human)	980	3947	6544	10 491
Therapeutic substance—approved drug (veterinary medicine)	16	0	362	362
Therapeutic substance—drug class	41	51	139	190
Therapeutic substance—investigational drug	30	118	47	165
Dietary substance (all)	103	42	267	309
Dietary substance—artificial sweeteners	5	6	14	20
Dietary substance—dietary Compounds	72	46	138	184
Dietary substance—drinks	20	1	80	81
Dietary substance—foods	13	0	34	34
Herbal substance (all)	119	367	547	914
Herbal substance—medicinal herb	24	2	115	117
Herbal substance—medicinal herbal compounds	87	364	405	769
Herbal substance—TCM formula	5	0	24	24
Environmental substance (all)	142	37	716	753
Environmental substance—heavy metals	10	4	158	162
Environmental substance—persistent organic pollutants	14	0	94	94
Environmental substance—pesticides	26	0	269	269

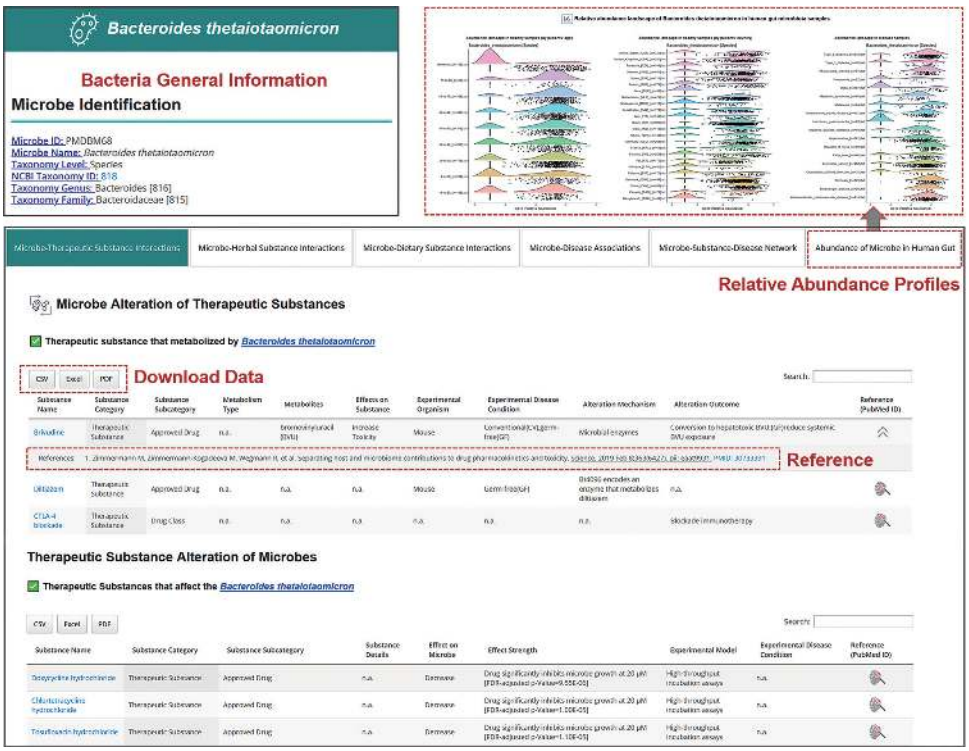

Figure 2. An example webpage of microbiota species. The top section provides taxonomic classification of the bacteria species. Microbiota–active substance interaction records are grouped into different categories and presented in individual tables. Users can click the fingerprint-like button in the 'Reference (PubMed ID)' column to see detailed information of each reference. All records shown in table can be downloaded via 'CSV', 'Excel' and 'PDF' download options in the left-top of each table. Detailed interaction data of substance can be accessed by clicking substance name in each row.

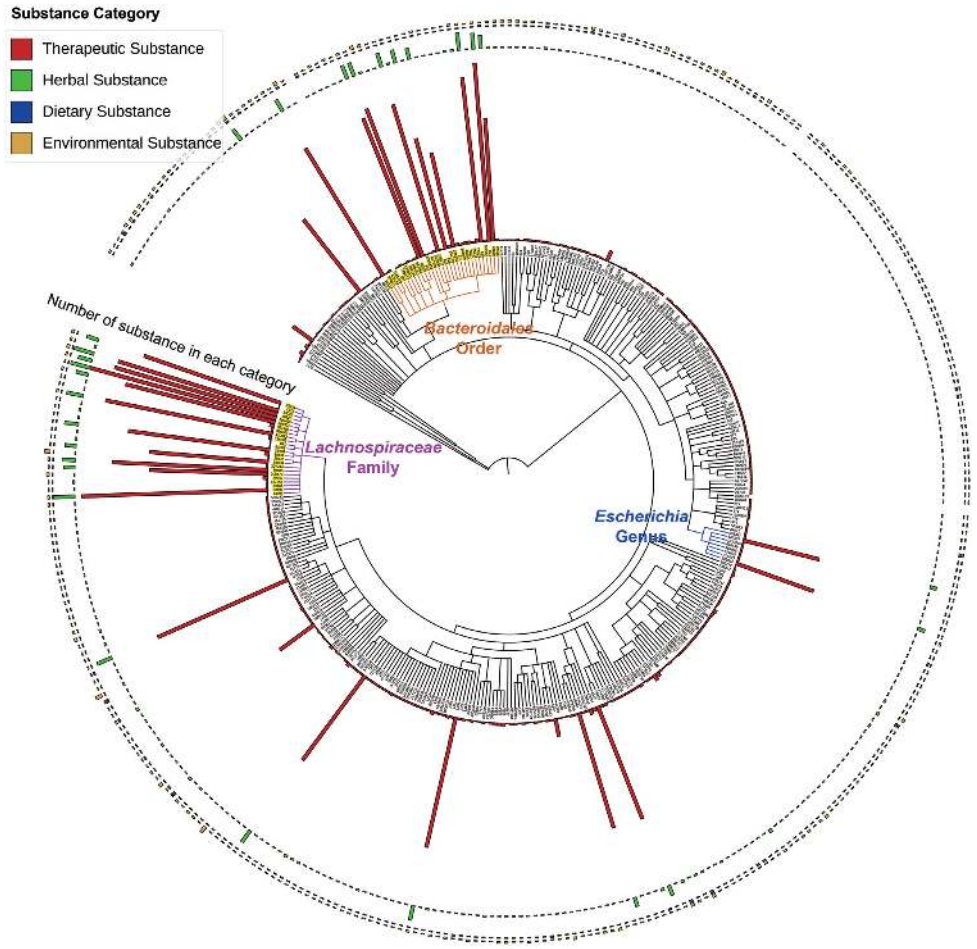

Figure 3. Active substance distribution in the phylogenetic tree of human microbiota species. 532 bacteria species with NCBI Taxonomic Identifier available were included in this tree. The number of substances of individual bacteria species ranges from 1 to 203. Phylogenetic tree of microbiota species was generated based on Taxonomy Identifiers using phyloT webserver and annotated and visualized by iTOL software (50).

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REFERENCES

1. Gould,A.L., Zhang,V., Lamberti,L., Jones,E.W., Obadia,B., Korasidis,N., Gavryushkin,A., Carlson,J.M., Beerenwinkel,N. and Ludington,W.B. (2018) Microbiome interactions shape host fitness. *Proc. Natl. Acad. Sci. U.S.A.*, **115**, E11951–E11960.
2. Koppel,N., Maini Rekdal,V. and Balskus,E.P. (2017) Chemical transformation of xenobiotics by the human gut microbiota. *Science*, **356**, eaag2770.
3. Clarke,G., Sandhu,K.V., Griffin,B.T., Dinan,T.G., Cryan,J.F. and Hyland,N.P. (2019) Gut reactions: breaking down xenobiotic-microbiome interactions. *Pharmacol. Rev.*, **71**, 198–224.
4. Rowland,I., Gibson,G., Heinken,A., Scott,K., Swann,J., Thiele,I. and Tuohy,K. (2018) Gut microbiota functions: metabolism of nutrients and other food components. *Eur. J. Nutr.*, **57**, 1–24.
5. Zimmermann,M., Zimmermann-Kogadeeva,M., Wegmann,R. and Goodman,A.L. (2019) Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature*, **570**, 462–467.
6. Weersma,R.K., Zhernakova,A. and Fu,J. (2020) Interaction between drugs and the gut microbiome. *Gut*, **69**, 1510–1519.
7. Xu,J., Chen,H.B. and Li,S.L. (2017) Understanding the molecular mechanisms of the interplay between herbal medicines and gut microbiota. *Med. Res. Rev.*, **37**, 1140–1185.
8. Chiu,K., Warner,G., Nowak,R.A., Flaws,J.A. and Mei,W. (2020) The impact of environmental chemicals on the gut microbiome. *Toxicol. Sci.*, **176**, 253–284.
9. Tasnim,N., Abulizi,N., Pither,J., Hart,M.M. and Gibson,D.L. (2017) Linking the gut microbial ecosystem with the environment: does gut health depend on where we live? *Front Microbiol*, **8**, 1935.
10. Chung,W.S., Walker,A.W., Louis,P., Parkhill,J., Vermeiren,J., Bosscher,D., Duncan,S.H. and Flint,H.J. (2016) Modulation of the human gut microbiota by dietary fibres occurs at the species level. *BMC Biol.*, **14**, 3.
11. Hemarajata,P. and Versalovic,J. (2013) Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol*, **6**, 39–51.

12. Nicolas,G.R. and Chang,P.V. (2019) Deciphering the chemical lexicon of host-gut microbiota interactions. *Trends Pharmacol. Sci.*, **40**, 430–445.
13. Zimmermann,M., Zimmermann-Kogadeeva,M., Wegmann,R. and Goodman,A.L. (2019) Separating host and microbiome contributions to drug pharmacokinetics and toxicity. *Science*, **363**, eaat9931.
14. Doestzada,M., Vila,A.V., Zhernakova,A., Koonen,D.P.Y., Weersma,R.K., Touw,D.J., Kuipers,F., Wijmenga,C. and Fu,J. (2018) Pharmacomicrobiomics: a novel route towards personalized medicine? *Protein Cell*, **9**, 432–445.
15. Colotti,G. and Rinaldi,T. (2020) The central role of gut microbiota in drug metabolism and personalized medicine. *Future Med Chem*, **12**, 1197–1200.
16. Aziz,R.K., Saad,R. and Rizkallah,M.R. (2011) PharmacoMicrobiomics or how bugs modulate drugs: an educational initiative to explore the effects of human microbiome on drugs. *BMC Bioinformatics*, **12**, A10.
17. Janssens,Y., Nielandt,J., Bronselaer,A., Debunne,N., Verbeke,F., Wynendaele,E., Van Immerseel,F., Vandewynckel,Y.P., De Tre,G. and De Spiegeleer,B. (2018) Disbiome database: linking the microbiome to disease. *BMC Microbiol.*, **18**, 50.
18. Noronha,A., Modamio,J., Jarosz,Y., Guerard,E., Sompairac,N., Preciat,G., Danielsdottir,A.D., Krecke,M., Merten,D., Haraldsdottir,H.S. *et al.* (2019) The Virtual Metabolic Human database: integrating human and gut microbiome metabolism with nutrition and disease. *Nucleic Acids Res.*, **47**, D614–D624.
19. Cheng,L., Qi,C., Zhuang,H., Fu,T. and Zhang,X. (2020) gutMDisorder: a comprehensive database for dysbiosis of the gut microbiota in disorders and interventions. *Nucleic Acids Res.*, **48**, D554–D560.
20. Sayers,E.W., Beck,J., Brister,J.R., Bolton,E.E., Canese,K., Comeau,D.C., Funk,K., Ketter,A., Kim,S., Kimchi,A. *et al.* (2020) Database resources of the National Center for Biotechnology Information. *Nucleic Acids Res.*, **48**, D9–D16.
21. Federhen,S. (2012) The NCBI Taxonomy database. *Nucleic Acids Res.*, **40**, D136–143.
22. Tao,L., Wang,B., Zhong,Y., Pow,S.H., Zeng,X., Qin,C., Zhang,P., Chen,S., He,W., Tan,Y. *et al.* (2017) Database and bioinformatics studies of probiotics. *J. Agric. Food Chem.*, **65**, 7599–7606.
23. Wang,Y., Bryant,S.H., Cheng,T., Wang,J., Gindulyte,A., Shoemaker,B.A., Thiessen,P.A., He,S. and Zhang,J. (2017) PubChem BioAssay: 2017 update. *Nucleic Acids Res.*, **45**, D955–D963.
24. O'Boyle,N.M., Banck,M., James,C.A., Morley,C., Vandermeersch,T. and Hutchison,G.R. (2011) Open Babel: an open chemical toolbox. *J Cheminform*, **3**, 33.
25. Wishart,D.S., Feunang,Y.D., Guo,A.C., Lo,E.J., Marcu,A., Grant,J.R., Sajed,T., Johnson,D., Li,C., Sayeeda,Z. *et al.* (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.*, **46**, D1074–D1082.
26. Shannon,P., Markiel,A., Ozier,O., Baliga,N.S., Wang,J.T., Ramage,D., Amin,N., Schwikowski,B. and Ideker,T. (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.*, **13**, 2498–2504.
27. Pasolli,E., Schiffer,L., Manghi,P., Renson,A., Obenchain,V., Truong,D.T., Beghini,F., Malik,F., Ramos,M., Dowd,J.B. *et al.* (2017) Accessible, curated metagenomic data through ExperimentHub. *Nat. Methods*, **14**, 1023–1024.
28. Maier,L., Pruteanu,M., Kuhn,M., Zeller,G., Telzerow,A., Anderson,E.E., Brochado,A.R., Fernandez,K.C., Dose,H., Mori,H. *et al.* (2018) Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*, **555**, 623–628.
29. McQuade,J.L., Daniel,C.R., Helmink,B.A. and Wargo,J.A. (2019) Modulating the microbiome to improve therapeutic response in cancer. *Lancet Oncol.*, **20**, e77–e91.
30. Lucafo,M., Franzin,M., Lagatolla,C., Franca,R., Bramuzzo,M., Stocco,G. and Decorti,G. (2020) Emerging insights on the interaction between anticancer and immunosuppressant drugs and intestinal microbiota in pediatric patients. *Clin Transl Sci*, **13**, 238–259.
31. Zimmermann,P. and Curtis,N. (2019) The effect of antibiotics on the composition of the intestinal microbiota - a systematic review. *J. Infect.*, **79**, 471–489.
32. Willing,B.P., Russell,S.L. and Finlay,B.B. (2011) Shifting the balance: antibiotic effects on host-microbiota mutualism. *Nat. Rev. Microbiol.*, **9**, 233–243.
33. Wu,X.M. and Tan,R.X. (2019) Interaction between gut microbiota and ethnomedicine constituents. *Nat. Prod. Rep.*, **36**, 788–809.
34. Dalile,B., Van Oudenhove,L., Vervliet,B. and Verbeke,K. (2019) The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat. Rev. Gastroenterol. Hepatol.*, **16**, 461–478.
35. Piwowarski,J.P., Granica,S., Stefanska,J. and Kiss,A.K. (2016) Differences in metabolism of ellagitannins by human gut microbiota ex vivo cultures. *J. Nat. Prod.*, **79**, 3022–3030.
36. Claus,S.P., Guillou,H. and Ellero-Simatos,S. (2016) The gut microbiota: a major player in the toxicity of environmental pollutants? *NPJ Biofilms Microbiomes*, **2**, 16003.
37. Sun,J., Liao,X.P., D'Souza,A.W., Boolchandani,M., Li,S.H., Cheng,K., Luis Martinez,J., Li,L., Feng,Y.J., Fang,L.X. *et al.* (2020) Environmental remodeling of human gut microbiota and antibiotic resistome in livestock farms. *Nat. Commun.*, **11**, 1427.
38. Javurek,A.B., Spollen,W.G., Johnson,S.A., Bivens,N.J., Bromert,K.H., Givan,S.A. and Rosenfeld,C.S. (2016) Effects of exposure to bisphenol A and ethinyl estradiol on the gut microbiota of parents and their offspring in a rodent model. *Gut Microbes*, **7**, 471–485.
39. Baxter,N.T., Zackular,J.P., Chen,G.Y. and Schloss,P.D. (2014) Structure of the gut microbiome following colonization with human feces determines colonic tumor burden. *Microbiome*, **2**, 20.
40. Weir,T.L., Manter,D.K., Sheflin,A.M., Barnett,B.A., Heuberger,A.L. and Ryan,E.P. (2013) Stool microbiome and metabolome differences between colorectal cancer patients and healthy adults. *PLoS One*, **8**, e70803.
41. Liddicoat,C., Sydnor,H., Cando-Dumancela,C., Dresken,R., Liu,J., Gellie,N.J.C., Mills,J.G., Young,J.M., Weyrich,L.S., Hutchinson,M.R. *et al.* (2020) Naturally-diverse airborne environmental microbial exposures modulate the gut microbiome and may provide anxiolytic benefits in mice. *Sci. Total Environ.*, **701**, 134684.
42. Schirmer,M., Smeekens,S.P., Vlamakis,H., Jaeger,M., Oosting,M., Franzosa,E.A., Ter Horst,R., Jansen,T., Jacobs,L., Bonder,M.J. *et al.* (2016) Linking the human gut microbiome to inflammatory cytokine production capacity. *Cell*, **167**, 1125–1136.
43. Gehrig,J.L., Venkatesh,S., Chang,H.W., Hibberd,M.C., Kung,V.L., Cheng,J., Chen,R.Y., Subramanian,S., Cowardin,C.A., Meier,M.F. *et al.* (2019) Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science*, **365**, eaau4732.
44. Iida,N., Dzutsev,A., Stewart,C.A., Smith,L., Bouladoux,N., Weingarten,R.A., Molina,D.A., Salcedo,R., Back,T., Cramer,S. *et al.* (2013) Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science*, **342**, 967–970.
45. Mendez,D., Gaulton,A., Bento,A.P., Chambers,J., De Veij,M., Felix,E., Magarinos,M.P., Mosquera,J.F., Mutowo,P., Nowotka,M. *et al.* (2019) ChEMBL: towards direct deposition of bioassay data. *Nucleic Acids Res.*, **47**, D930–D940.
46. Wang,Y., Zhang,S., Li,F., Zhou,Y., Zhang,Y., Wang,Z., Zhang,R., Zhu,J., Ren,Y., Tan,Y. *et al.* (2020) Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Res.*, **48**, D1031–D1041.
47. Zeng,X., Zhang,P., He,W., Qin,C., Chen,S., Tao,L., Wang,Y., Tan,Y., Gao,D., Wang,B. *et al.* (2018) NPASS: natural product activity and species source database for natural product research, discovery and tool development. *Nucleic Acids Res.*, **46**, D1217–D1222.
48. Zou,Y., Xue,W., Luo,G., Deng,Z., Qin,P., Guo,R., Sun,H., Xia,Y., Liang,S., Dai,Y. *et al.* (2019) 1,520 reference genomes from cultivated human gut bacteria enable functional microbiome analyses. *Nat. Biotechnol.*, **37**, 179–185.
49. Levy,R., Magis,A.T., Earls,J.C., Manor,O., Wilmanski,T., Lovejoy,J., Gibbons,S.M., Omenn,G.S., Hood,L. and Price,N.D. (2020) Longitudinal analysis reveals transition barriers between dominant ecological states in the gut microbiome. *Proc. Natl. Acad. Sci. U.S.A.*, **117**, 13839–13845.
50. Letunic,I. and Bork,P. (2019) Interactive Tree Of Life (iTOL) v4: recent updates and new developments. *Nucleic Acids Res.*, **47**, W256–W259.