

World Journal of *Clinical Cases*

World J Clin Cases 2022 March 26; 10(9): 2660-2975



Contents

Thrice Monthly Volume 10 Number 9 March 26, 2022

REVIEW

- 2660 Role of metabolites derived from gut microbiota in inflammatory bowel disease
Zheng L, Wen XL, Duan SL

MINIREVIEWS

- 2678 Roles of Wnt/ β -catenin signaling pathway related microRNAs in esophageal cancer
Chu CY, Wang R, Liu XL
- 2687 Animal models applied to acute-on-chronic liver failure: Are new models required to understand the human condition?
Gama JFG, Cardoso LMDF, Lagrota-Candido JM, Alves LA

ORIGINAL ARTICLE

Case Control Study

- 2700 Associations between coagulation factor XII, coagulation factor XI, and stability of venous thromboembolism: A case-control study
Meng Y, Li Y, Ye YJ, Ma Q, Zhang JB, Qin H, Deng YY, Tian HY

Retrospective Cohort Study

- 2710 Nomogram to predict the risk of endoscopic removal failure with forceps/baskets for treating submandibular stones
Huang Y, Liang PS, Yang YC, Cai WX, Tao Q
- 2721 Association between anesthesia technique and complications after hip surgery in the elderly population
Guo LS, Wang LN, Xiao JB, Zhong M, Zhao GF

Retrospective Study

- 2733 Perforating and nonperforating indications in repeated surgeries for Crohn's disease
Shen WS, Huang XH, Liu RQ, Li CY, Li Y, Zhu WM
- 2743 Treatment of *Pneumocystis jirovecii* pneumonia in non-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin
Wu HH, Fang SY, Chen YX, Feng LF
- 2751 Acute kidney injury in traumatic brain injury intensive care unit patients
Huang ZY, Liu Y, Huang HF, Huang SH, Wang JX, Tian JF, Zeng WX, Lv RG, Jiang S, Gao JL, Gao Y, Yu XX
- 2764 Enucleation combined with guided bone regeneration in small and medium-sized odontogenic jaw cysts
Cao YT, Gu QH, Wang YW, Jiang Q

Clinical Trials Study

- 2773 Determination of the ED₉₅ of intranasal sufentanil combined with intranasal dexmedetomidine for moderate sedation during endoscopic ultrasonography

Zou Y, Li N, Shao LJZ, Liu FK, Xue FS, Tao X

Observational Study

- 2783 Overexpression of Ubiquilin4 is associated with poor prognosis in patients with cervical cancer

Wang LN, Huang KJ, Wang L, Cheng HY

Randomized Clinical Trial

- 2792 Peplau's interpersonal relationship theory combined with bladder function training on patients with prostate cancer

Yang XH, Wu LF, Yan XY, Zhou Y, Liu X

SYSTEMATIC REVIEWS

- 2801 Efficacy of bone grafts in jaw cystic lesions: A systematic review

Wang J, Yao QY, Zhu HY

CASE REPORT

- 2811 Short stature associated with a novel mutation in the aggrecan gene: A case report and literature review

Yin LP, Zheng HX, Zhu H

- 2818 Treatment with sorafenib plus camrelizumab after splenectomy for primary splenic angiosarcoma with liver metastasis: A case report and literature review

Pan D, Li TP, Xiong JH, Wang SB, Chen YX, Li JF, Xiao Q

- 2829 Sarcomatoid intrahepatic cholangiocarcinoma with good patient prognosis after treatment with Huaier granules following hepatectomy: A case report

Feng JY, Li XP, Wu ZY, Ying LP, Xin C, Dai ZZ, Shen Y, Wu YF

- 2836 Sequential occurrence of T790M mutation and small cell lung cancer transformation in EGFR-positive lung adenocarcinoma: A case report

Hong E, Chen XE, Mao J, Zhou JJ, Chen L, Xu JY, Tao W

- 2844 Early diagnosis of Gitelman syndrome in a young child: A case report

Wu CY, Tsai MH, Chen CC, Kao CH

- 2851 Congenital intestinal malrotation with gastric wall defects causing extensive gut necrosis and short gut syndrome: A case report

Wang Y, Gu Y, Ma D, Guo WX, Zhang YF

- 2858 Delusional parasitosis as premotor symptom of parkinson's disease: A case report

Oh M, Kim JW, Lee SM

- 2864** Laninamivir-induced ischemic enterocolitis: A case report
Suzuki C, Kenzaka T
- 2871** Intramural pregnancy after *in vitro* fertilization and embryo transfer: A case report
Xie QJ, Li X, Ni DY, Ji H, Zhao C, Ling XF
- 2878** Bilateral ureteral reimplantation in a patient with an intraperitoneal ectopic bipenis: A case report
Jia YT, Shi BL, Zhang J, Li YY, Zhu J
- 2883** Lumbar disc sequestration mimicking a tumor: Report of four cases and a literature review
Li ST, Zhang T, Shi XW, Liu H, Yang CW, Zhen P, Li SK
- 2895** Parasitic leiomyoma in the trocar site after laparoscopic myomectomy: A case report
Roh CK, Kwon HJ, Jung MJ
- 2901** Giant nontraumatic myositis ossificans in a child: A case report
Xia AN, Wang JS
- 2908** Paradoxical carbon dioxide embolism during laparoscopic hepatectomy without intracardiac shunt: A case report
Jeon S, Hong JM, Lee HJ, Kim Y, Kang H, Hwang BY, Lee D, Jung YH
- 2916** Local hyperthermia combined with chemotherapy for the treatment of multiple recurrences of undifferentiated pleomorphic sarcoma: A case report
Zhou YT, Wang RY, Zhang Y, Li DY, Yu J
- 2923** Acute coronary artery stent thrombosis caused by a spasm: A case report
Meng LP, Wang P, Peng F
- 2931** Turner syndrome with primary myelofibrosis, cirrhosis and ovarian cystic mass: A case report
Xu LW, Su YZ, Tao HF
- 2938** Esophageal myoepithelial carcinoma: Four case reports
Lu H, Zhao HP, Liu YY, Yu J, Wang R, Gao JB
- 2948** Ipsilateral hemifacial microsomia with dextrocardia and pulmonary hypoplasia: A case report
Guo R, Chang SH, Wang BQ, Zhang QG
- 2954** Upper gastrointestinal bleeding from a Mallory-Weiss tear associated with transesophageal echocardiography during successful cardiopulmonary resuscitation: A case report
Tang MM, Fang DF, Liu B
- 2961** Malignant struma ovarii with papillary carcinoma combined with retroperitoneal lymph node metastasis: A case report
Xiao W, Zhou JR, Chen D

- 2969** Occult colon cancer with sepsis as the primary manifestation identified by bone marrow puncture: A case report

Wang HJ, Zhou CJ

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Arunchai Chang, MD, Assistant Professor, Lecturer, Staff Physician, Division of Gastroenterology, Department of Internal Medicine, Hatyai Hospital, Hatyai 90110, Songkhla, Thailand. busmdcu58@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*, Production Department Director: *Xiang Li*, Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

March 26, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Role of metabolites derived from gut microbiota in inflammatory bowel disease

Lie Zheng, Xin-Li Wen, Sheng-Lei Duan

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Rimondi A, Sassaki LY

Received: October 12, 2021

Peer-review started: October 12, 2021

First decision: December 3, 2021

Revised: December 12, 2021

Accepted: February 27, 2022

Article in press: February 27, 2022

Published online: March 26, 2022



Lie Zheng, Xin-Li Wen, Sheng-Lei Duan, Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, Xi'an 710003, Shaanxi Province, China

Corresponding author: Sheng-Lei Duan, MD, Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, No. 4 Xihuamen, Xi'an 710003, Shaanxi Province, China. 281930369@qq.com

Abstract

Over the past two decades, it is improved gut microbiota plays an important role in the health and disease pathogenesis. Metabolites, small molecules produced as intermediate or end products of microbial metabolism, is considered as one of the major interaction way for gut microbiota with the host. Bacterial metabolisms of dietary substrates, modification of host molecules or bacteria are the major source of metabolites. Signals from microbial metabolites affect immune maturation and homeostasis, host energy metabolism as well as mucosal integrity maintenance. Based on many researches, the composition and function of the microbiota can be changed, which is also seen in the metabolite profiles of patients with inflammatory bowel disease (IBD). Additionally, some specific classes of metabolites also can trigger IBD. In this paper, definition of the key classes of microbial-derived metabolites which are changed in IBD, description of the pathophysiological basis of association and identification of the precision therapeutic modulation in the future are the major contents.

Key Words: Inflammatory bowel disease; Microbial metabolites; Short chain fatty acids; Bile acids; Tryptophan

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In the gastrointestinal tract of the human, a variety of microorganisms such as bacteria, fungi, viruses, archaea and protozoa are collected and considered as a community, containing a genome, suitable to the environment and the host. Microbiome, with wide functions, can ferment dietary fibres, defence pathogen, synthesize vitamin and promote immune maturation and metabolic homeostasis, which indicates microbiome is deeply integrated with human biology. However, because gut microbiota is associated with ancestral diet high in fibre, the dietary alteration resulted from western diet causes maladaptive change for this association, and products of microbial metabolism exist at a nexus between host and microbiome.

Citation: Zheng L, Wen XL, Duan SL. Role of metabolites derived from gut microbiota in inflammatory bowel disease. *World J Clin Cases* 2022; 10(9): 2660-2677

URL: <https://www.wjgnet.com/2307-8960/full/v10/i9/2660.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i9.2660>

INTRODUCTION

In recent years, metabolomics based evaluation system has been used to search for biomarkers of inflammatory bowel disease (IBD) and explore its pathogenesis. It is becoming an important method of IBD research[1]. In the gastrointestinal tract of the human, a variety of microorganisms such as bacteria, fungi, viruses, archaea and protozoa are collected and considered as a community, containing a genome, suitable to the environment and the host[2]. Microbiome can ferment dietary fibres, defence pathogen, synthesize vitamin and promote immune maturation and metabolic homeostasis, which indicates microbiome is deeply integrated with human biology[3]. However, because gut microbiota is associated with ancestral diet high in fibre, the dietary alteration resulted from western diet causes maladaptive change for this association[4].

Researchers have begun to investigate the metabolites of IBD using metabolomics to explain the undetermined etiology and improve treatment outcomes[5]. In terms of diagnosis and evaluation, to date, there is no reliable laboratory test that can distinguish between the two subtypes of IBD, namely ulcerative colitis and Crohn's disease; Conventional inflammatory hematological indicators, such as platelet parameters, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), can be used to judge the correlation with IBD inflammatory activity and predict treatment effect and prognosis[6]. However, such tests cannot screen IBD patients in a timely and effective manner. Therefore, new biomarkers for IBD are still being sought, and the emergence of metabolomics techniques can help better analyze and solve these key questions.

As an integral part of systems biology, metabolomics is a method of quantitative analysis of all metabolites in a living organism, imitating the research ideas of genomics and proteomics, and searching for the relative relationship between metabolites and physiological and pathological changes [7]. The research objects are mostly small molecules with a relative molecular weight of less than 1000.

Microbial metabolites are found in a variety of biological tissues such as faeces, urine, serum, and have diversified effects on these host physiology[8]. IBD patients can be classified based on the alterations in faecal, urinary and serum metabolomes, which shows a new mechanism and association is found[9]. Additionally, several metabolite classes become the key research, for finding the association with intestinal inflammation and IBD, such as bile acid derivatives[10]. It is noted that these may affect the host, and association is found among the host, dysbiotic microbiota and an altered metabolite milieu through the inflammation model involving diet, genetic risk and the microbiota[11].

A metabolome is a collection of metabolites in a cell, tissue, or organ, consisting of a series of molecules of different chemical types, such as peptides, carbohydrates, lipids, nucleic acids, and the catalytic products of foreign substances[12]. Metabolomics studies evaluate the effects of exogenous stimuli and explore their mechanisms by quantitatively analyzing the changes of endogenous metabolites in biological systems[13]. Complete metabolomics includes sample collection and preparation; Detection and identification of metabolites; Data analysis and modeling; To establish the relationship between temporal and spatial variation of metabolites and characteristics of organisms[14]. Metabonomics is the genomics, proteomics, transcriptome study after emerging "omics", metabonomics has the advantage of the medium and small molecular substances is the study of the biology to produce the final results and metabolism, while genome and proteome have a cumulative and compensation effect, they are effective tiny changes in metabolites is amplified, therefore, The identification of metabolites is easier and more accurate to reflect the state of biological system[15].

In this review, the characteristics description of gut metabolome, and the description of the integration of metabolomics with other data are involved[16]. Furthermore, untargeted researches of IBD, targeted metabolomics with the focus on short chain fatty acids (SCFAs), bile acids and tryptophan metabolism are included[17]. In final, small molecule discovery, diagnostic potential and therapeutic manipulation of the gut microbiome-metabolome axis as the future directions is discussed[18].

CHARACTERIZATION OF THE GUT METABOLOME

Metabolites are comprehensive products of physiological processes, and metabolic phenotypes can reflect the organism's life state. Metabolomics technology reflects the body's response to physiological stimulation or gene modification through qualitative and quantitative analysis of real-time changes in endogenous substances[19]. Compared with other omics, it detects a relatively small number of substances, but amplifies small differences at the level of genes and proteins. At the same time, effectively reduce the interference of inactive genes and inactive proteins, higher accuracy. Therefore, metabolomics has developed rapidly in the last 20 years[20].

The human body is a super organism composed of host and microorganism. Intestinal flora participates in absorption, metabolism, immunity, defense and maintenance of intestinal stability[21]. However, for a long time, the important role of intestinal flora in maintaining human balance has been underestimated due to the large variety and number, complex interrelationship and lack of efficient and convenient analysis methods[22]. In addition to maintaining intestinal homeostasis through self-formation of mucosal barrier and multi-signaling pathway regulation, co-metabolites of host and intestinal flora are also a major regulation mode. Intestinal flora participates in host metabolism, producing a large number of small molecules and hormones, and metabolites enter the host body to participate in body circulation and affect host homeostasis[23]. For example, flagellin and lipopolysaccharide produced by intestinal flora regulate human fat metabolism through nuclear factor interleukin-3 and biological clock, so intestinal flora is both metabolic participant and regulator[24]. Changes in metabolites can also predict abnormalities in the gut microbiota, For example, the increase of organic acid content in urine suggests that *Clostridium difficile*, *Faecalibacterium prausnitzii* and *Bifidobacterium SPP.*, *Subdoligranulum SPP.*, and *Lactobacillus SPP*[25].

For metabolomics, there are several analytical techniques and platforms on the basis of mass spectrometry [26]. Metabolomics research strategies can be pursued in either targeted or untargeted ways. Targeted metabolomics accurately quantifies a group of known metabolites, whereas untargeted approaches cover as many metabolites as possible[27].

Metabolomics has the advantages of high throughput, high accuracy and high sensitivity, which can detect the changes of small molecule metabolites produced by the body in the dynamic process of metabolism qualitatively or quantitatively[28]. The analysis process of metabolomics includes three parts: sample preparation, data collection and data analysis and interpretation[29]. The samples for metabolomics analysis are mainly biological specimens, which are commonly used in urine, blood, saliva, feces extract, and local pathological tissues such as colon tissue. The metabolites in the samples are usually ¹H-NMR and gas chromatography[30].

Gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry (LIQUID chromatography-mass spectrometry) Lc-ms) and other methods. Bioinformatics platform is used for data processing for data analysis and interpretation, and principal Component analysis (PCA) is the most commonly used method[31]. PCA and Partial least squares discriminant analysis (PLS-DA). Since the 1990s. Since the emergence of the late Era, metabolomics has been widely used in the study of drug toxicity and mechanism, microbial and plant metabolomics, nutrition science and disease diagnosis and other fields[32].

Notably, attention should be taken to the untargeted metabolomics, though this method is a promising method to discover program[33]. Firstly, no universal method exists in sample preprocessing and extraction, particular methods in allusion to particular families of metabolites[34]. As a result, several methods can be combined. Consequently, considering different sample matrix and molecules, extraction methods show different efficacy so that it is difficult to obtain precise quantification. Secondly, there are various pitfalls when spectral data from mass spectrometry experiments are converted into to chemically annotated compounds[35]. According to different levels of evidences, various compounds are still classified as unknowns[36]. To understand them, it requires manual expertise and computational algorithms. Thirdly, it is not enough to take databases such as Metlin as the references, because it only contains a small fraction of compounds[37]. Based on estimation, higher than 90% of spectral features in a microbiome study is not known. But, according to a recent study, a molecular class can be assigned from Human Metabolome Database based on 43% of metabolite features[38]. Additionally, it is a great challenge to annotate the unknown compound. Finally, various intermediate- or low-concentration compounds or proximally produced ones in the intestine, can not be well represented in the faecal metabolome[39]. Consequently, special requirements in the sample collection and standardization, annotation and data integration at a systematic biology level as well as careful design are needed when integrating discovery projects that incorporate untargeted metabolomics with other omics technologies[40].

However, targeted metabolomics own several strongpoints in extraction, known internal standards and more precise absolute quantification, even though it is limited to spectrum[41].

UNTARGETED METABOLOMICS IN IBD

A large number of untargeted faecal metabolomic researches among the patients with IBD are published [42]. Though these researches involve different groups, including adults and children, and different subtypes and using different metabolomics approaches, some common themes are considered [43]. Metabolomics can be used to classify the groups who are healthy and with IBD [44]. However, metabolomics is not an ideal approach to discriminate Crohn's disease and ulcerative colitis.

From metabolite group, the description of dysregulation of bile acid metabolism, changes in the levels of amino acids, sphingolipids, polyamines and reductions in levels of medium-chain fatty acids and SCFAs is consistent in faecal samples [45]. At the same time, variation in the metabolome is associated with the variation of microbiome between the healthy subjects and patients groups [46].

Bile acids can be divided into primary bile acids and secondary bile acids according to their sources, and free bile acids and conjugated bile acids according to their structural types [47]. Primary bile acids are produced in the liver and bind to taurine or glycine to form the corresponding conjugated bile acids, which are then released into the gallbladder by bile Salt export Pump for storage and further concentration [48]. After eating, bile acids are released into the duodenum, facilitating emulsification and absorption of lipids in the small intestine. At the terminal ileum, about 95% of the bile acids are reabsorbed and returned to the liver *via* the portal vein [49]. The cycle in which bile acids are secreted from the liver to the intestine, reabsorbed in the ileum, and then returned to the liver *via* the portal vein is called hepatenteric circulation. 400-800 mg of unabsorbed bile acids enter the colon daily for further dissociation, hydroxylation, differential isomerization, and dehydroxylation, and the enzymes catalyzing these reactions are mostly produced by intestinal microorganisms [50]. The biliary saline hydrolysates involved in bile acid dissociation are mainly produced by *Bacteroides*, *Clostridium*, *Lactobacillus*, *Bifidobacterium* and *Listeria*. Dehydrogenase or heteroisomerase involved in Bile acids oxidation or heteroisomerase reaction are mainly *Bacteroides*, *Eubacterium*, *Clostridium*, *Escherichia*, *Eggerthella*, *Peptostreptococcus* and *Ruminococcus* [51]. A series of reactions of bile acids in colon play an important role in maintaining the diversity and dynamic balance of bile acid pools. It is worth noting that bile acids can also affect the composition of intestinal microorganisms through bacteriostasis while intestinal microorganisms produce enzymes catalyzing the metabolism of bile acids [52].

The pathogenesis of IBD is not completely clear, genetic factors and environmental factors are important factors leading to mucosal immune response disorders. With the development of metabolomics, the researchers observed significant changes in a variety of metabolites in IBD patients compared with healthy subjects, such as fecal amino acids, bile acids, sphingomyelic acid, medium chain fatty acids, short chain fatty acids, and polyamines [53]. The change of intestinal bile acid profile is closely related to the development of IBD. A study involving 155 patients with IBD and 65 healthy controls showed that more than 2700 metabolites differed between patients with IBD and healthy people [54]. The metabolites of IBD patients were mainly manifested as sphingolipids and bile acids, while the bile acids enriched in feces of IBD patients were mainly conjugated bile acids and sulphated bile acids, while the content of secondary bile acids decreased. The analysis of serum bile acid content in patients with IBD showed that the serum bile acid metabolism was disorder, especially the secondary bile acid content in patients with active stage was significantly reduced [55].

The diversity of intestinal bile acids is closely related to intestinal microbes. Although the causal relationship between intestinal flora and IBD is still unclear, the disorder of bile acid metabolism in IBD patients is often accompanied by changes in intestinal microbial composition [56]. The diversity of intestinal flora in IBD patients decreased, and the composition ratio of intestinal flora also changed, which was mainly manifested as the decreased abundance of *Firmicutes* [57]. The proportion of *Clostridia* changed significantly, the abundance of *Roseburia* and *Faecalibacterium* decreased, while that of *Ruminococcus gnavus* increased. The ratio of *Faecalibacterium prausnitzii* and *Escherichia coli* decreased. In turn, increased bile acid content in the gut promotes the growth of biliary tolerant bacteria such as *Bilophila Wadsworthii* and promotes TH1-mediated mucosal immune response [58].

Untargeted metabolomics researches are also carried out among the human biological samples, involving urine, serum and/or plasma and intestinal biopsy samples [59]. Compared with control group, the level of urinary mammalian-microbial co-metabolite hippurate is reduced, and tricarboxylic acid cycle intermediates and amino acid metabolism in IBD group are altered [60]. Generally, it is possible to distinguish the healthy subjects and the controlled ones, even though it is not completely clear to know the differences between metabolomes of patients with Crohn's disease and those with ulcerative colitis [61].

The new research results involve loss of secondary bile acids, vitamins B3 and B5 and SCFAs, and expansion of acylcarnitines and polyunsaturated fatty acids [62]. But, it is found that the result is associated with dysbiotic subset of samples. This dysbiotic subset was defined as being outside the ninetieth percentile of the healthy cohort, and 'excursions' into this state were weakly correlated with inflammatory activity [63]. This indicates that multimodal functional assessment is important in explaining the longitudinal relationship, with a higher understanding than a single classification [64]. The study on the mechanism in the future can answer the question of clinical relevance involving the determination of biomarkers of treatment response and disease course [65].

TARGETED METABOLOMICS IN IBD

Biles acids

Bile acids are synthesized from cholesterol by the liver in a multi-enzyme process, involving two products[66]. These primary bile acids exhibit amphipathic properties, which are beneficial for the lipid digestion and absorption in the small intestine[67]. When reaching the distal ileum, 95% of them are reabsorbed, and the rest is recycled and replaced, which are controlled by fibroblast growth factor[68]. Bile acids not only can regulate own synthesis, but also can exert many metabolic and immune effects through binding a series of receptors such as farnesoid X receptor (FXR), TGR5 as well as constitutive androstane receptor[69]. TGR5 is beneficial for improving insulin sensitivity, reduce energy expenditure in muscle and brown adipose tissue, and relax the gallbladder[70]. TGR5 also reduces Kupffer cell response to lipopolysaccharide by nuclear factor- κ B inhibition and release of IL-1, IL-6 and tumor necrosis factor (TNF) from peripheral blood monocytes in humans. Activation of FXR has diverse effects on host metabolism[71].

Hepatic bile acid synthesis is regulated by the FXR-FGF15/19 signaling pathway. Activation of this signaling pathway reduces the expression of enzymes related to hepatic bile acid synthesis and reduces bile acid synthesis[72]. It has been found that reduced FGF19 levels in Crohn's disease (CD) patients lead to reduced activation of FXR, which inhibits the FXR-FGF15/19 pathway and leads to increased bile acid synthesis in the liver, leading to the development of intestinal inflammation[73]. Therefore, compared with the normal population, the enterohepatic circulation is blocked in IBD patients, and the activation of signal pathways that negatively regulate the synthesis of intrahepatic bile acids is reduced, leading to an increase in the total amount of bile acids in the intestinal lumen, which is also one of the causes of intestinal inflammation[73].

Restoration of bile acid pools was found to increase colon ROR γ Treg cell numbers and improve host susceptibility to inflammatory colitis through bile acid nuclear receptors[74]. Recent studies have shown that ursodeoxycholic acid, as a candidate drug for nonalcoholic fatty liver disease[75], can improve intestinal barrier function, reduce intestinal inflammation, and regulate intestinal microbiota composition. Ursodeoxycholic acid and its metabolite, shicholic acid, can reduce the severity of intestinal inflammation and inhibit the expression of mucosal cytokines in a DSS-induced mouse model of colitis[76]. It has also been found that ursodeoxycholic acid and shicholic acid can inhibit the cleavage of caspase-3, a protease related to colon epithelial apoptosis[77]. Therefore, ursodeoxycholic acid may improve intestinal inflammation by inhibiting the apoptosis of epithelial cells. However, long-term high dose (28-30 mg/kg/d) ursodeoxycholic acid exposure is not protective for Ulcerative colitis (UC) patients and may increase the risk of colorectal cancer[78]. The role of ursodeoxycholic acid in the treatment of IBD is still controversial and has not been confirmed by strong clinical evidence, so further studies are needed.

Although some reports suggest that secondary bile acids such as deoxycholic acid and shicholic acid may be cytotoxic molecules that cause oxidative stress, membrane damage, interference with DNA repair, mucosal inflammation and colon cancer[79], some studies have found that *Clostridium hiranonis* promotes the production of secondary bile acids[80]. Relieves DSS-induced colitis because secondary bile acids at physiological concentrations inhibit the growth of *E. coli* and *B. perfringens in vitro*[81]. *Clostridium scindens* may also be involved in the induction of CD relief in children by producing secondary bile acids. Therefore, secondary bile acids may be a promising therapeutic agent for IBD and deserve further study[82].

MICROBIALY TRANSFORMED BILE ACIDS IN IBD

The pathogenesis of IBD is related to genetics, environment, intestinal microecology and immunity, but the specific biological mechanism is still unclear. As an important part of intestinal microecology, intestinal flora can directly affect intestinal environmental homeostasis and participate in bile acid metabolism, while the abnormal bile acid metabolism also affects the quality and quantity of intestinal flora, and both of them are involved in the occurrence and development of intestinal inflammation[83].

For IBD patients, due to bile acid malabsorption and the inherently bidirectional nature of such interaction, it is not easy to observe the effect of dysbiosis on bile acid dysmetabolism[84]. Some researchers including Devkota carry out a ground-breaking study find that the proportion of taurine-conjugated bile acids in the mice with the diet high in milk-derived fat is higher than that in the ones with low-fat diet, which leads to the bloom of *B. wadsworthia*[85]. Due to the development of colitis, the change happens on IL10 $^{-/-}$ mice, which indicates that western diet, altered host metabolites, dysbiosis are associated with inflammation in the genetically susceptible host[86].

Recent studies have found that bile acids are a powerful driver of intestinal microbiota maturation in newborns[87]. The effects of bile acids on intestinal flora are bidirectional, promoting the growth of bacteria dependent on bile acid metabolism on the one hand, and inhibiting the growth of bacteria sensitive to bile on the other hand[88]. Bile acids have a direct lactating effect on bacterial cell membranes and can also play an antibacterial role by activating the synthesis of antimicrobial

substances mediated by FXR[89]. FXR is expressed in liver, intestine, fat, vascular wall, pancreas, kidney and other tissues[90]. Activation of intestinal FXR can induce the encoding of antimicrobial target genes including angiogenin, carbonic anhydrase 12 and inducible nitric oxide synthase, thus exerting antibacterial effect[91]. In the process of deoxycholic acid induced intestinal inflammation, the diversity of intestinal flora decreased significantly[92]. At the level of bacteroidetes, the proportion of Firmicutes increased while the proportion of Bacteroidetes decreased. At the genus level, the proportion of Bacteroidetes increased, while the proportion of *Clostridium* XIVa decreased, indicating that high concentration of deoxycholic acid could aggravate the imbalance of intestinal flora[93].

Additionally, using synthetic agonist to directly stimulating FXR shows anti-inflammatory effect, and shows protection function in chemically induced colitis, but susceptibility to chemical injury is increased as the result of FXR^{-/-} mice exhibit[94]. It should be noted that if microbial bile acid metabolizing genes is lost, the cell subtype *in vivo* may be reduced[95].

Repeated exposure of intestinal epithelial cells to high concentrations of bile acids is an important risk factor for IBD, and IBD patients have high levels of deoxycholic acid in the intestine[96]. In rats with colitis induced by Trinitrobenzenesulfonic acid (TNBS), apical sodium-dependent bile acid transporter (ASBT) expression decreased[97]. In IBD patients, ileal inflammation blocks hepatointestinal circulation of bile acids, leading to reduced ileal reabsorption, which may be due to inhibition of ASBT promoter expression by inflammatory cytokines, thus increasing fecal bile acids[98].

In recent years, intestinal flora has been regarded as an "endocrine organ" that regulates host physiological functions by producing metabolites such as bile acids and short-chain fatty acids. Bile acid metabolism mainly occurs in hepatocytes and intestinal flora[99].

Animal studies have shown that deoxycholic acid reduces intestinal abundance of *Clostridium*, a species that produces bile acid hydrolases that convert Tauro-Muricholic acid into cholic acid[100]. The decrease of this genus resulted in the accumulation of taurocholic acid, which is an FXR antagonist and inhibits the FXR-mediated signaling pathway[101]. FXR interacts with downstream fibroblast growth factor15/19 (FGF15/19) to regulate bile acid metabolism through the enterohepatic signaling pathway[102]. Once FXR and FGF15/19 signal pathways are interfered, the intestinal liver circulation of bile acids in the body is disturbed, resulting in increased bile acid levels in the intestinal lumen. High concentration of bile acids can promote the occurrence of gastrointestinal inflammation by damaging the DNA of intestinal cells[103].

In many studies, the altered faecal bile acid in IBD is described repeatedly. Considering potential confounders, Ganesan *et al*[104] perform a study and focus on the patients with isolated colonic IBD. Recent studies have shown that deoxycholic acid mediates intestinal ecological imbalance, damages the intestinal mucosal barrier, and ultimately leads to intestinal inflammation. The disturbance of intestinal microbiome - bile acid dialogue can damage intestinal barrier function and activate inflammatory signaling pathway, leading to the occurrence and development of intestinal inflammation[105].

TRYPTOPHAN

Through eating poultry, fish and dairy foods, the humans obtain tryptophan. This is an essential, aromatic amino acid and the precursor for the synthesis of several important bioactive molecules. Tryptophan metabolism is mainly produced in the gastrointestinal tract[106]. Amino acids play an important role in keeping your gut healthy. Tryptophan is an essential amino acid associated with autoimmune, and its metabolic pathway is related to the pathogenesis of inflammatory bowel disease[107].

Dietary tryptophan can be metabolized by intestinal flora into a series of indole-metabolites, such as indole-acetic acid, indole-3-acetaldehyde, indole-3-aldehydes, indole-acrylics, and indole-3-propionic acid, which act as ligands for aromatic hydrocarbon receptors, which have been implicated in the pathogenesis of IBD[108]. Indoles, indoles propionic acid and indoles acrylic acid may reduce intestinal permeability and affect mucosal homeostasis by binding progesterone X receptor. Indoleformaldehyde can activate aromatic hydrocarbon receptors on intestinal immune cells and increase IL-22 production. Indole derivatives bind to aromatic hydrocarbon receptors to produce IL-10, so oral indole-3-propionic acid protects mice from DSS-induced colitis[108]. Therefore, the disorder of intestinal flora can destroy immune regulation through its metabolites and promote the progress of intestinal inflammation.

Dietary tryptophan follows one of three main routes, and the majority is metabolized in the kynurenine pathway. and its rate-limiting enzymes include indoleamine 2,3-dioxygenase 1 in mucosal and immune cells and tryptophan 2,3-dioxygenase in the liver[109]. Serotonin pathway is considered as the second major host route, of which, the rate-limiting enzyme tryptophan hydroxylase 1 in enterochromaffin cell plays a controlled role. In final, tryptophan can be metabolized by the gut microbiota into a range of indole metabolites[110]. It is important that microbiota and microbial metabolite also play a regulation role for both host tryptophan pathways[111].

In allusion to metabolites from gut microbiome, GLP1 is released due to the stimulation of indole, but indole derivatives can act as agonists for AhR. Diet-derived AhR agonists has a great effect on maintaining the microbial load and composition and immune tolerance in the proximal small intestine

[112]. On contrary, in the distal small intestine and colon, microbiota-derived AhR agonists has a great effect. Existing researches show that limited amount of bacteria can produce AhR agonists, whereas when *C. sporogenes* is produced, which triggers IPA. Its production is associated with fldAIBC phenyllactate gene cluster, beneficial for maintaining barrier function and inhibiting mucosal TNF production [113].

TRYPTOPHAN METABOLISM

A study involving 535 patients with IBD shows that tryptophan metabolism is increased, and disease activity is inversely correlated with tryptophan levels[114]. Based on this analysis, it is suggested metabolism is increased through kynurenine pathway[115]. The result is also observed in the previous studies. Previous studies have reported that the expression of AhR in inflamed mucosal samples from patients with Crohn's disease is decreased, and lack of dietary tryptophan has the association with worsening colitis in mouse models[116].

Tryptophan is one of the eight essential amino acids in the human body. When tryptophan is ingested, it enters different metabolic pathways, including protein anabolism and tryptophan catabolism[117]. The tryptophan catabolism pathway includes: 5-HT pathway (about 95%), canisurine pathway (about 1%-2%), and bacterial decomposition pathway[118]. These pathways work together to maintain the balance of the body's environment and keep the body healthy. At the same time, as a drug, tryptophan is widely used in the treatment of many diseases[119]. For example, tryptophan supplementation can reduce mood swings and irritability in women with premenstrual syndrome, improve sleep quality in patients with sleep disorders, treat depression, and may be used as an adjunct therapy for smokers to quit smoking. Recent studies have confirmed that the metabolic pathway of tryptophan regulates gastrointestinal function[120], and changes in tryptophan metabolism can lead to gastrointestinal dysfunction and disease, such as inflammatory bowel disease, irritable bowel syndrome, celiac disease and diverticulitis. In previous studies, tryptophan levels in UC patients were significantly lower than those in healthy volunteers. The same results were seen in UC animal models. However, the researchers did not make a strict distinction between the active stage and the remission stage[121]. By comparing the differences of tryptophan in different periods of UC patients (active stage, remission stage) and healthy volunteers, this study further demonstrated that tryptophan plays a key role in the occurrence and development of UC[122]. In the experiment, we also found that serum tryptophan level was negatively correlated with inflammatory markers ESR and CRP in active UC patients ($P < 0.05$). Based on the changes of serum tryptophan in active and remission stages of UC, as well as the correlation between serum tryptophan level in active stage and inflammatory markers, serum tryptophan level in patients with UC may have important significance for monitoring the activity of UC. This also fully demonstrates the value of tryptophan in UC research[123].

Additionally, researchers carry out a research to examine the effect of mucin-utilizing bacteria, and confirm that commensal *P. russellii* plays a role in reducing the susceptibility to colitis by metabolizing tryptophan to IA, through which, goblet cell differentiation is improved and inflammatory signal is reduced[124]. The same pathway occurs for IA in *P. russellii*. A novel finding that fldAIBC phenyllactate gene cluster was also identified in *P. russellii* is described. This is a new finding, making a link between a bacterium with mucin- and tryptophan-metabolizing abilities to improved epithelial integrity, so that the researchers can know the decrease in phenyllactate gene cluster in ulcerative colitis in the condition of metagenomics study involving IBD and non-IBD control individuals[125].

Intestinal flora involved in tryptophan metabolism is also an important signal pathway to regulate the immune system. It has been confirmed that tryptophan metabolism is weakened in the absence of intestinal bacteria, which is manifested as increased tryptophan content and decreased active metabolites. Intestinal tryptophan metabolites can regulate the activity of Aryl hydrocarbon receptor (AhR) in immune cells, which is a key factor to maintain immune balance[126]. AhR can effectively balance T regulatory cells and Th17. Indole is a product of tryptophan expressed by enterobacteriaceae tryptophan enzyme, which can protect the integrity of intestinal bacterial membrane, reduce the adhesion of pathogenic bacteria, promote the production of anti-inflammatory factor interleukin-10, and reduce the production of inflammatory factors. Indole-3-propionic acid (INDOLE-3-PROPIONIC ACID) is a product of indoles under the action of intestinal flora, and its production requires the participation of *Clostridium sporogenes*. Indole-3-propionic acid can inhibit inflammatory signals through progesterone X receptors and improve the integrity of the intestinal barrier[127].

SCFAs

SCFAs is a kind of beneficial metabolite and derived from microbiota-accessible carbohydrates[128]. After microbial fermentation, acetate, propionate and butyrate are produced, also other gases such as gases methane and hydrogen sulfide are included[129]. Different diets affect the proportions 50%-70% for acetate, 10%-20% for propionate and the biggest for butyrate. In allusion to dietary intervention, if the humans take more animal-based diets, the protein fermentation is rapidly changed and dysbiosis is caused[130].

SCFAs are organic fatty acids composed of one to six carbon atoms. The main production site of SCFAs is the colon. SCFAs are mostly produced by the enzymatic hydrolysis of carbohydrates in undigested and absorbed food residues by anaerobic bacteria in the colon, mainly including acetic acid, propionic acid and butyric acid, with a concentration of about 20-140 in the colon. The type and quantity of mmol/L. scfAs were mainly determined by the composition of intestinal flora, digestion time, host-microbial metabolic flux and fiber content in host food[131]. SCFAs produced by fermentation participate in the metabolism of different organs in human body and play different functions. Acetic acid produced by bacterial fermentation can be absorbed and utilized by the host and is an important source of host energy, providing about 10% of the total daily energy of the human body. After absorbed by blood, propionic acid catabolizes in the liver, participating in the process of pyruvate reversal into glucose, and may inhibit the synthesis of fat; Butyric acid is mainly used by epithelial cells and is the main energy source of epithelial cells[132].

Notably, it is observed typical dysbiosis in IBD is correlated with the lost bacterial species, which is consistent with the general result that faecal SCFA level is reduced in the metabolomics studies of human IBD[133]. If the section of colon is surgically failed, diversion colitis is caused and can be treated with SCFA enemas. Butyrate by enema is effective to treat ulcerative colitis to a certain degree, and butyrate-producing dietary fibre additives may be beneficial for the maintenance of remission[134].

SCFAs and IBD

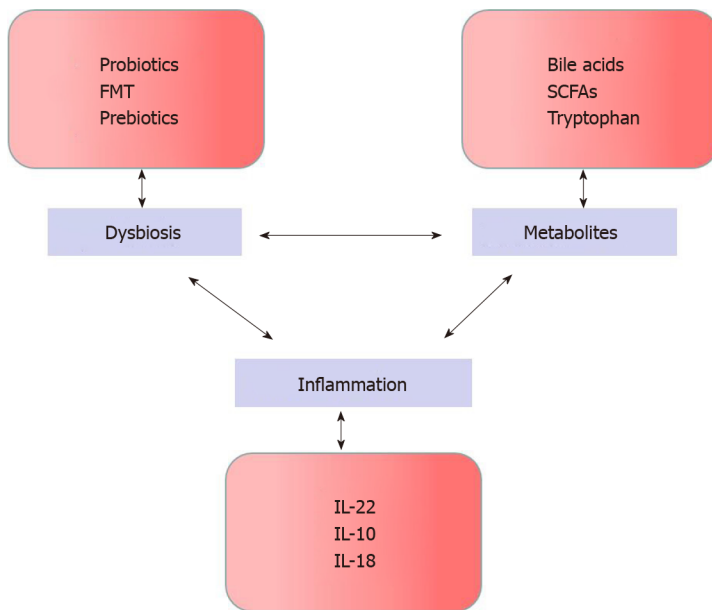
If the butyrate-producing species in IBD patients is lost, it is observed that butyrate oxidation is impaired. On the basis of some researches, among the patients with IBD, the level of faecal SCFAs is reduced at different degrees[135]. This result is consistent with the research on the quantitative PCR targeting the butyryl-CoA: Acetate-CoA-transferase gene[136]. While the result for active ulcerative colitis and Crohn's disease indicates that the intermediate molecule lactate is increased[137]. But, due to the fact that only approximately 5% of SCFAs remain in faeces, there is no significant difference in the alterations in transit, absorption and utilization between the controlled subjects and healthy ones[138]. As a result, to know that anti-inflammatory associations with butyrate-producing bacteria may be caused by other mechanisms is also beneficial for the further study[139].

SCFAs are endogenous substances that have been widely studied for the correlation between IBD metabolomics and intestinal flora. SCFAs are products of indigestible carbohydrates under the action of *Clostridium plusseri*, *Rothberry*, *Eubacterium* and *Bifidobacteria*, mainly including acetic acid, propionic acid, butyric acid and isobutyric acid[140]. The content of SCFAs in feces can reflect the status of intestinal flora. It has been reported that the fecal butyric acid, isobutyric acid and acetic acid in patients with active IBD decreased significantly, and the contents of *Clostridium coccoides*, *Clostridium leptum*, *Clostridium pralei* and *R.i. Ntestinalis* decreased. Correlation analysis showed that butyric-producing bacteria *Clostridium plerii* and *enterorothburiae* were positively correlated with butyric acid, isobutyric acid and acetic acid, while abnormal enterobacteria tended to be normal during remission[141]. Therefore, this study suggested that the decrease of SCFAs content caused by intestinal flora disturbance was related to the incidence of IBD. The abnormal metabolism of butyric acid, which is the energy source of colon epithelial cells, and acetic acid, which is involved in adipogenesis and gluconeogenesis, suggests that inflammation leads to disturbance of intestinal energy metabolism. Acetic acid and butyric acid exert anti-inflammatory effects by activating G protein receptor 41 (GPR41) and GPR43 and inhibiting histone deacetylases. Regulating intestinal production of short-chain fatty acids has become a new target for the treatment of IBD[142].

According to a mouse study, the association between the low level and dietary fibre and susceptibility to dextran sulfate sodium (DSS)-induced colitis is constructed, in which, diet-derived SCFAs plays an important role[143]. Based on the result of DSS model, if the fatty acid receptor GPR43 in mice is lost, refractory colitis is triggered[144]. The same finding is seen in the constituents of the gut microbiota[145]. It is indicated that overactivation of the NLRP1A receptor in mice leads to loss of butyrate-producing Clostridiales, with increased IL-18 and IFN γ production[146]. In final, it is observed the gene expression of NLRP1 in inflamed regions of the distal colon in patients with ulcerative colitis is increased, and a majority of bacterial operational taxonomic units were of the order Clostridiales, which is consistent with the mechanistic observation in a human cohort[147] (Figure 1).

OTHER ASSOCIATED METABOLITES

Fatty acids showed significant changes in faeces of UC patients, including a significant decrease in short chain fatty acids (SCFA, such as acetic acid, propionic acid and butyric acid) and medium chain fatty acids (valeric acid, hexanoic acid, heptanic acid, captanic acid and nonanoic acid)[148]. Fatty acids participate in energy supply through β -oxidation, and butyric acid oxidation can provide 60% energy for colon cells, again suggesting abnormal energy metabolism in UC state. SCFA plays an anti-inflammatory role through tumor necrosis factor α and NF- κ B pathways and the activation of GPR41 and GPR43. The decrease of SCFA induced by inflammation can make inflammation persist. Medium chain fatty acids activate peroxisome proliferators to activate receptors for anti-inflammatory effects[149].



DOI: 10.12998/wjcc.v10.i9.2660 Copyright ©The Author(s) 2022.

Figure 1 The cycle of circular causality in inflammatory bowel disease. FMT: Fecal microbiota transplantation; SCFAs: Short chain fatty acids.

Methylamine, trimethylamine, and trimethylamine oxide are products of choline action by gastrointestinal flora, and their reduction indicates that choline metabolism is disturbed[150]. Choline is an important component of cell membrane and the key to maintaining cell membrane integrity. Choline increases in feces of UC patients, while glycerophosphoryl choline decreases as a choline metabolite, indicating that the integrity of intestinal cell membrane changes in UC patients and inflammation may lead to intestinal mucosal damage[151]. Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) are products of fat metabolism in the liver. The decrease in serum levels of both is caused by inflammation that increases the activity of phospholipase A2, promotes the hydrolysis of phospholipids in LDL and VLDL, and inhibits the expression of lipase that hydrolyzes triglycerides[152].

Succinate metabolism in IBD is a promising direction. Succinate is the intermediate of host cells and the microbiota. In the host, succinate acts as an important pro-inflammatory signal and has been shown to be a key mediator, *via* IL-1 β , of macrophage response to lipopolysaccharide[153]. For the patients with Crohn's disease, the level of succinate in the serum is increased, and increased result is obtained for the expression of the SUCNR1, *Sucnr1*^{-/-} mice are protected against fibrosis and 2,4,6-trinitrobenzene sulfonic acid-induced colitis[154]. On contrary, the level of urinary succinate among the IBD patients is decreased, lower than that of the controlled subjects[155]. The level of faecal succinate in the patients with ulcerative colitis and Crohn's disease is higher than that in the subjects with no IBD and in DSS-induced colitis at the peak period of weight loss[156]. It is analyzed from the perspective of microbiota that succinate-utilizing *Phascolarctobacterium* is less abundant in both ulcerative colitis and Crohn's disease than in healthy subjects. Some researchers make efforts to find the effect of important metabolite and the role of gut microbiota[157].

FUTURE DIRECTIONS

Small-molecule discovery

The family involving G protein-coupled receptor (GPCR) ligands, N-acyl amides, is identified[158]. These are encoded by the microbiota and that are agonists to receptors that have important implications for gastrointestinal and metabolic physiology, such as the endocannabinoid receptor GPR119[159]. A study carried out by Settanni *et al*[160] uses bioinformatics mining to identify biologically conserved gene clusters in metagenomes by the computational and synthetic biology pipeline.

Using another different 'chemistry forward' method and relying on a high-throughput GPCR reporter platform, human gut microbiota is derived from 11 patients with IBD, aiming to identify relevant metabolites. This study not only identify the activation of GPCRs in a wide range based on the constituents analysis of the human gut microbiota, but also identify *Morganella morganii* converted the aromatic amino acid L-phenylalanine into phenethylamine, and the clear *in vivo* association between *M. morganii*-produced and *Lactobacillus reuteri*-produced histamine and colonic transit time[161]. By relying on Human Microbiome Project dataset, these research results are obtained based on the deep mining of metagenomic assemblies, so as to determine the increase level of histidine decarboxylase genes in the

patients with Crohn's disease[162]. Using these methods, information as well as techniques from different sources to examine the microbiota for novel compounds, it is of great significance to identify bioactive molecules relevant to IBD[162].

THERAPEUTIC OPTIONS

Next-generation probiotics. Studies have shown that dysbiosis has the association with disease, which motivate the researchers to perform combined therapy involving the host process and microbiome[163]. Intestinal probiotics *Akkermansia muciniphila* can induce homeostasis IgG production and antigen-specific T cell response in mice, regulate immune homeostasis, and improve the symptoms of DSS induced colitis in mice.

A recent study found that a hydrolyzed protein diet alleviates DSS-induced colitis by regulating the imbalance of intestinal flora and increasing the production of secondary bile acids by *Clostridium hiranonis*[164]. Other studies found that exogenous fucose can significantly reduce the inflammatory response of DSS colitis mice, and it was found that after the administration of fucose, the imbalance of intestinal flora was improved, so as to restore the normal synthesis of bile acid pools in the body and liver, and then reduce the colitis of mice.

However, potential next-generation probiotics (NGPs) involve commensals in the gut of adults, so researchers pay more attention to its metabolite production. Candidate NGPs, according to the identification of its role in specific condition based on the analysis of gut microbiome, is featured with fastidiousness, or extreme sensitiveness of oxygen[165]. As a result, how to isolate, cultivate characterize and formulate them is of a great challenge. It is possible for NGPs and other similar products performed with evaluation under the regulation of LBP, so that investigation for the new drug procedures based on FDA152 is required[165].

In the previous studies, the potential of targeted microbiome-metabolite therapeutics in the form of the colonization resistance is found[162]. Some studies show *C. difficile* spore germination receptor binds to the primary bile acid CA derivatives and is inhibited by the secondary bile acid deoxycholic acid (DCA). When *C. scindens* to mice at risk of *Clostridium difficile* infection (CDI) is administrated, the resistance to CDI is improved[162].

Faecal microbiota transplantation

It is interesting that bile acid profiles show marked alteration in CDI and restored after successful fecal microbiota transplantation (FMT) which is effective in treating recurred CDI[158]. Some studies demonstrate that FMT is effective in reducing the remission in ulcerative colitis. Fecal microbiota transplantation is the transplantation of faecal flora from a healthy donor into the gastrointestinal tract of a patient and can correct IBD-related intestinal flora disorders. Some scholars have found that fecal bacteria transplantation may be a safe and effective method for the treatment of refractory CD. Six weeks after receiving fecal bacteria transplantation, the severity index of Crohn's disease under endoscopy decreased significantly with CD, and the level of C-reactive protein also decreased significantly compared with the control group[162]. Patients who were in remission after fecal bacteria transplantation had more *Eubacterium Hallii* and *Roseburia Inulinivorans* in their faeces and colon, which increased short-chain fatty acid biosynthesis and secondary bile acid levels. Specific bacterial and metabolic pathways in fecal bacteria transplantation are involved in inducing remission, and these findings may be of great reference value for the design of microbial therapies for IBD. The sample size may also affect the experimental results. Therefore, whether fecal transplantation is effective in alleviating symptoms of IBD patients needs to be verified by clinical studies with larger samples.

Metabolites

LBP is a partially attractive due to its ability in getting high concentration of metabolites in the intestine, so oral metabolites or their precursors may be a great challenge in pharmacology[154]. At present, a placebo-controlled, crossover trial in allusion to tryptophan metabolites is undergoing, aiming to determine the efficiency of oral 5-hydroxytryptophan administration on fatigue among the patients with IBD[165]. For diabetes, niacin is delivered to the gut microbiota by microcapsules, which indicates that the level of gut Bacteroidetes is increased, and the marker of insulin resistance in healthy control volunteers is improved. This is an interesting finding, which demonstrates some preclinical and clinical promise is effective in treating ulcerative colitis.

CONCLUSION

Based on analysis involving technology, observational data and experimental insight, it is illuminated that microbial metabolites is beneficial for the pathogenesis of IBD. With the change of lifestyle and dietary pattern, the incidence of IBD is increasing year by year. High-fat diet changes the intestinal

microecological homeostasis and also affects the metabolism of bile acids in the body, so that the role of the dialogue mechanism between intestinal flora and bile acids in gastrointestinal diseases has attracted more and more attention. In conclusion, existing studies have shown that intestinal flora imbalance or bile acid metabolism disorder caused by various external factors can make intestinal flora, bile acid metabolism and IBD form a vicious circle of mutual influence. For the prevention and treatment of IBD, it is necessary to further explore the mechanism of intestinal flora, bile acids and their receptors in IBD. The scientific and reasonable application of probiotics, antibiotics, bile acids and their derivatives to prevent IBD will be the key problem to be solved in the future.

In this review, untargeted metabolomics and microbiome analyses are summarized, suggesting that the pattern of alteration for metabolite profiles is consisted. Among of them, bile acids, SCFAs and tryptophan metabolites are analyzed in details. This study emphasizes the unknowns in the faecal metabolome, so creating large multinational cohorts of patients with IBD and controls, and of pipelines for microorganism-metabolite discovery and evaluation is encouraged. From the perspective of future direction, some promising fields are identified to achieve the objective. It is noted that how to integrate dietary and targeted microbiota manipulation or even microbiota reconstitution to realize the goals is a great challenge. Gut microbiota-derived metabolites is possible to become a promising direction.

FOOTNOTES

Author contributions: Zheng L and Duan SL performed to the writing, revising of the manuscript; Zheng L and Wen XL contributed to design this work, and performed overall supervision; Zheng L wrote and revised the paper.

Supported by Shaanxi Province Natural Science Basic Research Program-General Project, No: 2019JM-580 and 2021SF-314; Project of Shaanxi Administration of Traditional Chinese Medicine, No. 2019-ZZ-JC010; Shaanxi Provincial Hospital of Traditional Chinese Medicine, No. 2018-04.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Lie Zheng 0000-0002-8243-3736; Xin-Li Wen 0000-0001-5003-862X; Sheng-Lei Duan 0000-0002-4151-1718.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES

- 1 Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res* 2017; **179**: 204-222 [PMID: 27591027 DOI: 10.1016/j.trsl.2016.08.002]
- 2 Wilkinson EM, Ilhan ZE, Herbst-Kralovetz MM. Microbiota-drug interactions: Impact on metabolism and efficacy of therapeutics. *Maturitas* 2018; **112**: 53-63 [PMID: 29704918 DOI: 10.1016/j.maturitas.2018.03.012]
- 3 Khalsa J, Duffy LC, Riscuta G, Starke-Reed P, Hubbard VS. Omics for Understanding the Gut-Liver-Microbiome Axis and Precision Medicine. *Clin Pharmacol Drug Dev* 2017; **6**: 176-185 [PMID: 28263462 DOI: 10.1002/cpdd.310]
- 4 David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; **505**: 559-563 [PMID: 24336217 DOI: 10.1038/nature12820]
- 5 Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015; **519**: 92-96 [PMID: 25731162 DOI: 10.1038/nature14232]
- 6 Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]
- 7 Etienne-Mesmin L, Chassaing B, Gewirtz AT. Tryptophan: A gut microbiota-derived metabolites regulating inflammation. *World J Gastrointest Pharmacol Ther* 2017; **8**: 7-9 [PMID: 28217370 DOI: 10.4292/wjgpt.v8.i1.7]
- 8 Krishnan S, Ding Y, Saeedi N, Choi M, Sridharan GV, Sherr DH, Yarmush ML, Alaniz RC, Jayaraman A, Lee K. Gut

- Microbiota-Derived Tryptophan Metabolites Modulate Inflammatory Response in Hepatocytes and Macrophages. *Cell Rep* 2018; **23**: 1099-1111 [PMID: 29694888 DOI: 10.1016/j.celrep.2018.03.109]
- 9 Bringer MA, Gabrielle PH, Bron AM, Creuzot-Garcher C, Acar N. The gut microbiota in retinal diseases. *Exp Eye Res* 2022; **214**: 108867 [PMID: 34856206 DOI: 10.1016/j.exer.2021.108867]
 - 10 Ding Y, Yanagi K, Cheng C, Alaniz RC, Lee K, Jayaraman A. Interactions between gut microbiota and non-alcoholic liver disease: The role of microbiota-derived metabolites. *Pharmacol Res* 2019; **141**: 521-529 [PMID: 30660825 DOI: 10.1016/j.phrs.2019.01.029]
 - 11 Del Rio D, Zimetti F, Caffarra P, Tassotti M, Bernini F, Brighenti F, Zini A, Zanotti I. The Gut Microbial Metabolite Trimethylamine-N-Oxide Is Present in Human Cerebrospinal Fluid. *Nutrients* 2017; **9** [PMID: 28937600 DOI: 10.3390/nu9101053]
 - 12 Claus SP, Tsang TM, Wang Y, Cloarec O, Skordi E, Martin FP, Rezzi S, Ross A, Kochhar S, Holmes E, Nicholson JK. Systemic multicompartmental effects of the gut microbiome on mouse metabolic phenotypes. *Mol Syst Biol* 2008; **4**: 219 [PMID: 18854818 DOI: 10.1038/msb.2008.56]
 - 13 Dodd D, Spitzer MH, Van Treuren W, Merrill BD, Hryckowian AJ, Higginbottom SK, Le A, Cowan TM, Nolan GP, Fischbach MA, Sonnenburg JL. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. *Nature* 2017; **551**: 648-652 [PMID: 29168502 DOI: 10.1038/nature24661]
 - 14 Nielsen LN, Roager HM, Casas ME, Frandsen HL, Gosewinkel U, Bester K, Licht TR, Hendriksen NB, Bahl MI. Glyphosate has limited short-term effects on commensal bacterial community composition in the gut environment due to sufficient aromatic amino acid levels. *Environ Pollut* 2018; **233**: 364-376 [PMID: 29096310 DOI: 10.1016/j.envpol.2017.10.016]
 - 15 Liu Y, Hou Y, Wang G, Zheng X, Hao H. Gut Microbial Metabolites of Aromatic Amino Acids as Signals in Host-Microbe Interplay. *Trends Endocrinol Metab* 2020; **31**: 818-834 [PMID: 32284282 DOI: 10.1016/j.tem.2020.02.012]
 - 16 Krishnan S, Alden N, Lee K. Pathways and functions of gut microbiota metabolism impacting host physiology. *Curr Opin Biotechnol* 2015; **36**: 137-145 [PMID: 26340103 DOI: 10.1016/j.copbio.2015.08.015]
 - 17 Maes M, Vojdani A, Geffard M, Moreira EG, Barbosa DS, Michelin AP, Semeão LO, Sirivichayakul S, Kanchanatawan B. Schizophrenia phenomenology comprises a bifactorial general severity and a single-group factor, which are differently associated with neurotoxic immune and immune-regulatory pathways. *Biomol Concepts* 2019; **10**: 209-225 [PMID: 31734647 DOI: 10.1515/bmc-2019-0023]
 - 18 Zierer J, Jackson MA, Kastenmüller G, Mangino M, Long T, Telenti A, Mohny RP, Small KS, Bell JT, Steves CJ, Valdes AM, Spector TD, Menni C. The fecal metabolome as a functional readout of the gut microbiome. *Nat Genet* 2018; **50**: 790-795 [PMID: 29808030 DOI: 10.1038/s41588-018-0135-7]
 - 19 Jain A, Li XH, Chen WN. An untargeted fecal and urine metabolomics analysis of the interplay between the gut microbiome, diet and human metabolism in Indian and Chinese adults. *Sci Rep* 2019; **9**: 9191 [PMID: 31235863 DOI: 10.1038/s41598-019-45640-y]
 - 20 Knight R, Vrbanc A, Taylor BC, Aksenov A, Callewaert C, Debelius J, Gonzalez A, Kosciolk T, McCall LI, McDonald D, Melnik AV, Morton JT, Navas J, Quinn RA, Sanders JG, Swafford AD, Thompson LR, Tripathi A, Xu ZZ, Zaneveld JR, Zhu Q, Caporaso JG, Dorrestein PC. Best practices for analysing microbiomes. *Nat Rev Microbiol* 2018; **16**: 410-422 [PMID: 29795328 DOI: 10.1038/s41579-018-0029-9]
 - 21 Lawson CE, Harcombe WR, Hatzenpichler R, Lindemann SR, Löffler FE, O'Malley MA, García Martín H, Pfleger BF, Raskin L, Venturelli OS, Weissbrodt DG, Noguera DR, McMahon KD. Common principles and best practices for engineering microbiomes. *Nat Rev Microbiol* 2019; **17**: 725-741 [PMID: 31548653 DOI: 10.1038/s41579-019-0255-9]
 - 22 Parra-Llorca A, Gormaz M, Alcántara C, Cernada M, Nuñez-Ramiro A, Vento M, Collado MC. Preterm Gut Microbiome Depending on Feeding Type: Significance of Donor Human Milk. *Front Microbiol* 2018; **9**: 1376 [PMID: 29997594 DOI: 10.3389/fmicb.2018.01376]
 - 23 Lakshmanan V, Ray P, Craven KD. Rhizosphere Sampling Protocols for Microbiome (16S/18S/ITS rRNA) Library Preparation and Enrichment for the Isolation of Drought Tolerance-Promoting Microbes. *Methods Mol Biol* 2017; **1631**: 349-362 [PMID: 28735410 DOI: 10.1007/978-1-4939-7136-7_23]
 - 24 Miyoshi J, Matsuura M, Hisamatsu T. Safety evaluation of ustekinumab for moderate-to-severe ulcerative colitis. *Expert Opin Drug Saf* 2022; **21**: 1-8 [PMID: 34511011 DOI: 10.1080/14740338.2021.1980536]
 - 25 Shade A, Dunivin TK, Choi J, Teal TK, Howe AC. Strategies for Building Computing Skills To Support Microbiome Analysis: a Five-Year Perspective from the EDAMAME Workshop. *mSystems* 2019; **4** [PMID: 31431509 DOI: 10.1128/mSystems.00297-19]
 - 26 Dheilly NM, Bolnick D, Bordenstein S, Brindley PJ, Figuères C, Holmes EC, Martínez Martínez J, Phillips AJ, Poulin R, Rosario K. Parasite Microbiome Project: Systematic Investigation of Microbiome Dynamics within and across Parasite-Host Interactions. *mSystems* 2017; **2** [PMID: 28761932 DOI: 10.1128/mSystems.00050-17]
 - 27 Heimann TM, Swaminathan S, Slater GI, Kurtz RJ. Perianal Fistula After Ileoanal Pouch in Patients With Ulcerative Colitis: A Review of 475 Patients Operated on at a Major IBD Center. *Dis Colon Rectum* 2022; **65**: 76-82 [PMID: 34882630 DOI: 10.1097/DCR.0000000000002114]
 - 28 Sandborn WJ, Danese S. Ozanimod for Ulcerative Colitis. Reply. *N Engl J Med* 2022; **386**: 194-195 [PMID: 35020995 DOI: 10.1056/NEJMc2117224]
 - 29 Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014; **6**: 1489-1499 [DOI: 10.1053/j.gastro.2014.02.009]
 - 30 Kho ZY, Lal SK. The Human Gut Microbiome - A Potential Controller of Wellness and Disease. *Front Microbiol* 2018; **9**: 1835 [PMID: 30154767 DOI: 10.3389/fmicb.2018.01835]
 - 31 Tsugawa H. Advances in computational metabolomics and databases deepen the understanding of metabolisms. *Curr Opin Biotechnol* 2018; **54**: 10-17 [PMID: 29413746 DOI: 10.1016/j.copbio.2018.01.008]
 - 32 Barko PC, McMichael MA, Swanson KS, Williams DA. The Gastrointestinal Microbiome: A Review. *J Vet Intern Med* 2018; **1**: 9-25 [DOI: 10.1111/jvim.14875]
 - 33 Li DS, Huang QF, Guan LH, Zhang HZ, Li X, Fu KL, Chen YX, Wan JB, Huang M, Bi HC. Targeted bile acids and gut

- microbiome profiles reveal the hepato-protective effect of WZ tablet (*Schisandra sphenanthera* extract) against LCA-induced cholestasis. *Chin J Nat Med* 2020; **18**: 211-218 [PMID: [32245591](#) DOI: [10.1016/S1875-5364\(20\)30023-6](#)]
- 34 **Yin S**, Guo P, Hai D, Xu L, Shu J, Zhang W, Khan MI, Kurland IJ, Qiu Y, Liu Y. Optimization of GC/TOF MS analysis conditions for assessing host-gut microbiota metabolic interactions: Chinese rhubarb alters fecal aromatic amino acids and phenol metabolism. *Anal Chim Acta* 2017; **995**: 21-33 [PMID: [29126478](#) DOI: [10.1016/j.aca.2017.09.042](#)]
 - 35 **Schönfeld P**, Wojtczak L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J Lipid Res* 2016; **57**: 943-954 [PMID: [27080715](#) DOI: [10.1194/jlr.R067629](#)]
 - 36 **Miyagawa Y**, Mori T, Goto K, Kawahara I, Fujiwara-Tani R, Kishi S, Sasaki T, Fujii K, Ohmori H, Kuniyasu H. Intake of medium-chain fatty acids induces myocardial oxidative stress and atrophy. *Lipids Health Dis* 2018; **17**: 258 [PMID: [30447697](#) DOI: [10.1186/s12944-018-0908-0](#)]
 - 37 **Lyudinina AY**, Ivankova GE, Bojko ER. Priority use of medium-chain fatty acids during high-intensity exercise in cross-country skiers. *J Int Soc Sports Nutr* 2018; **15**: 57 [PMID: [30526607](#) DOI: [10.1186/s12970-018-0265-4](#)]
 - 38 **Yunus IS**, Jones PR. Photosynthesis-dependent biosynthesis of medium chain-length fatty acids and alcohols. *Metab Eng* 2018; **49**: 59-68 [PMID: [30055323](#) DOI: [10.1016/j.ymben.2018.07.015](#)]
 - 39 **Lloyd-Price J**, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, Andrews E, Ajami NJ, Bonham KS, Brislawn CJ, Casero D, Courtney H, Gonzalez A, Graeber TG, Hall AB, Lake K, Landers CJ, Mallick H, Plichta DR, Prasad M, Rahnavard G, Sauk J, Shungin D, Vázquez-Baeza Y, White RA 3rd; IBDMDB Investigators, Braun J, Denson LA, Jansson JK, Knight R, Kugathasan S, McGovern DPB, Petrosino JF, Stappenbeck TS, Winter HS, Clish CB, Franzosa EA, Vlamakis H, Xavier RJ, Huttenhower C. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019; **569**: 655-662 [PMID: [31142855](#) DOI: [10.1038/s41586-019-1237-9](#)]
 - 40 **Aden K**, Rehman A, Waschina S, Pan WH, Walker A, Lucio M, Nunez AM, Bharti R, Zimmerman J, Bethge J, Schulte B, Schulte D, Franke A, Nikolaus S, Schroeder JO, Vandeputte D, Raes J, Szymczak S, Waetzig GH, Zeuner R, Schmitt-Kopplin P, Kaleta C, Schreiber S, Rosenstiel P. Metabolic Functions of Gut Microbes Associate With Efficacy of Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Diseases. *Gastroenterology* 2019; **157**: 1279-1292.e11 [PMID: [31326413](#) DOI: [10.1053/j.gastro.2019.07.025](#)]
 - 41 **Weng YJ**, Gan HY, Li X, Huang Y, Li ZC, Deng HM, Chen SZ, Zhou Y, Wang LS, Han YP, Tan YF, Song YJ, Du ZM, Liu YY, Wang Y, Qin N, Bai Y, Yang RF, Bi YJ, Zhi FC. Correlation of diet, microbiota and metabolite networks in inflammatory bowel disease. *J Dig Dis* 2019; **20**: 447-459 [PMID: [31240835](#) DOI: [10.1111/1751-2980.12795](#)]
 - 42 **Bjerrum JT**, Wang Y, Hao F, Coskun M, Ludwig C, Günther U, Nielsen OH. Metabonomics of human fecal extracts characterize ulcerative colitis, Crohn's disease and healthy individuals. *Metabolomics* 2015; **11**: 122-133 [PMID: [25598765](#) DOI: [10.1007/s11306-014-0677-3](#)]
 - 43 **Marchesi JR**, Holmes E, Khan F, Kochhar S, Scanlan P, Shanahan F, Wilson ID, Wang Y. Rapid and noninvasive metabonomic characterization of inflammatory bowel disease. *J Proteome Res* 2007; **6**: 546-551 [PMID: [17269711](#) DOI: [10.1021/pr060470d](#)]
 - 44 **Clerc F**, Novokmet M, Dotz V, Reiding KR, de Haan N, Kammeijer GSM, Dalebout H, Bladergroen MR, Vukovic F, Rapp E; IBD-BIOM Consortium, Targan SR, Barron G, Manetti N, Latiano A, McGovern DPB, Annesse V, Lauc G, Wuhler M. Plasma N-Glycan Signatures Are Associated With Features of Inflammatory Bowel Diseases. *Gastroenterology* 2018; **155**: 829-843 [PMID: [29792883](#) DOI: [10.1053/j.gastro.2018.05.030](#)]
 - 45 **Keshmeli AH**, van den Brand FF, Madsen KL, Mandal R, Valcheva R, Kroeker KI, Han B, Bell RC, Cole J, Hoevers T, Wishart DS, Fedorak RN, Dieleman LA. Dietary and metabolomic determinants of relapse in ulcerative colitis patients: A pilot prospective cohort study. *World J Gastroenterol* 2017; **23**: 3890-3899 [PMID: [28638229](#) DOI: [10.3748/wjg.v23.i21.3890](#)]
 - 46 **Dawiskiba T**, Deja S, Mulak A, Ząbek A, Jawień E, Pawełka D, Banasik M, Mastalerz-Migas A, Balcerzak W, Kaliszewski K, Skóra J, Barć P, Korta K, Pormańczuk K, Szyber P, Litarski A, Młynarz P. Serum and urine metabolomic fingerprinting in diagnostics of inflammatory bowel diseases. *World J Gastroenterol* 2014; **20**: 163-174 [PMID: [24415869](#) DOI: [10.3748/wjg.v20.i1.163](#)]
 - 47 **Daniluk U**, Daniluk J, Kucharski R, Kowalczyk T, Pietrowska K, Samczuk P, Filimoniuk A, Kretowski A, Lebensztejn D, Ciborowski M. Untargeted Metabolomics and Inflammatory Markers Profiling in Children With Crohn's Disease and Ulcerative Colitis-A Preliminary Study. *Inflamm Bowel Dis* 2019; **25**: 1120-1128 [PMID: [30772902](#) DOI: [10.1093/ibd/izy402](#)]
 - 48 **Sairenji T**, Collins KL, Evans DV. An Update on Inflammatory Bowel Disease. *Prim Care* 2017; **44**: 673-692 [PMID: [29132528](#) DOI: [10.1016/j.pop.2017.07.010](#)]
 - 49 **Abegunde AT**, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. *World J Gastroenterol* 2016; **22**: 6296-6317 [PMID: [27468219](#) DOI: [10.3748/wjg.v22.i27.6296](#)]
 - 50 **Hold GL**, Smith M, Grange C, Watt ER, El-Omar EM, Mukhopadhyay I. Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? *World J Gastroenterol* 2014; **20**: 1192-1210 [PMID: [24574795](#) DOI: [10.3748/wjg.v20.i5.1192](#)]
 - 51 **Scoville EA**, Allaman MM, Brown CT, Motley AK, Horst SN, Williams CS, Koyama T, Zhao Z, Adams DW, Beaulieu DB, Schwartz DA, Wilson KT, Coburn LA. Alterations in Lipid, Amino Acid, and Energy Metabolism Distinguish Crohn's Disease from Ulcerative Colitis and Control Subjects by Serum Metabolomic Profiling. *Metabolomics* 2018; **14**: 17 [PMID: [29681789](#) DOI: [10.1007/s11306-017-1311-y](#)]
 - 52 **Nishiumi S**, Izumi Y, Yoshida M. Alterations in Docosahexaenoic Acid-Related Lipid Cascades in Inflammatory Bowel Disease Model Mice. *Dig Dis Sci* 2018; **63**: 1485-1496 [PMID: [29564669](#) DOI: [10.1007/s10620-018-5025-4](#)]
 - 53 **Suh JH**, Degagné É, Gleghorn EE, Setty M, Rodriguez A, Park KT, Verstraete SG, Heyman MB, Patel AS, Irek M, Gildengorin GL, Hubbard NE, Borowsky AD, Saba JD. Sphingosine-1-Phosphate Signaling and Metabolism Gene Signature in Pediatric Inflammatory Bowel Disease: A Matched-case Control Pilot Study. *Inflamm Bowel Dis* 2018; **24**: 1321-1334 [PMID: [29788359](#) DOI: [10.1093/ibd/izy007](#)]
 - 54 **Wlodarska M**, Luo C, Kolde R, d'Hennezel E, Annand JW, Heim CE, Krastel P, Schmitt EK, Omar AS, Creasey EA, Garner AL, Mohammadi S, O'Connell DJ, Abubucker S, Arthur TD, Franzosa EA, Huttenhower C, Murphy LO, Haider

- HJ, Vlamakis H, Porter JA, Xavier RJ. Indoleacrylic Acid Produced by Commensal *Peptostreptococcus* Species Suppresses Inflammation. *Cell Host Microbe* 2017; **22**: 25-37.e6 [PMID: 28704649 DOI: 10.1016/j.chom.2017.06.007]
- 55 **Hall AB**, Yassour M, Sauk J, Garner A, Jiang X, Arthur T, Lagoudas GK, Vatanen T, Formelos N, Wilson R, Bertha M, Cohen M, Garber J, Khalili H, Gevers D, Ananthakrishnan AN, Kugathasan S, Lander ES, Blainey P, Vlamakis H, Xavier RJ, Huttenhower C. A novel *Ruminococcus gnavus* clade enriched in inflammatory bowel disease patients. *Genome Med* 2017; **9**: 103 [PMID: 29183332 DOI: 10.1186/s13073-017-0490-5]
- 56 **Yu LC**. Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis. *J Biomed Sci* 2018; **25**: 79 [PMID: 30413188 DOI: 10.1186/s12929-018-0483-8]
- 57 **Liu YJ**, Tang B, Wang FC, Tang L, Lei YY, Luo Y, Huang SJ, Yang M, Wu LY, Wang W, Liu S, Yang SM, Zhao XY. Parthenolide ameliorates colon inflammation through regulating Treg/Th17 balance in a gut microbiota-dependent manner. *Theranostics* 2020; **10**: 5225-5241 [PMID: 32373209 DOI: 10.7150/thno.43716]
- 58 **Vandana UK**, Barlasakar NH, Gulzar ABM, Laskar IH, Kumar D, Paul P, Pandey P, Mazumder PB. Linking gut microbiota with the human diseases. *Bioinformation* 2020; **16**: 196-208 [PMID: 32405173 DOI: 10.6026/97320630016196]
- 59 **Schulthess J**, Pandey S, Capitani M, Rue-Albrecht KC, Arnold I, Franchini F, Chomka A, Ilott NE, Johnston DGW, Pires E, McCullagh J, Sansom SN, Arancibia-Cárcamo CV, Uhlig HH, Powrie F. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages. *Immunity* 2019; **50**: 432-445.e7 [PMID: 30683619 DOI: 10.1016/j.immuni.2018.12.018]
- 60 **Larraufie P**, Martin-Gallausiaux C, Lapaque N, Dore J, Gribble FM, Reimann F, Blottiere HM. SCFAs strongly stimulate PYY production in human enteroendocrine cells. *Sci Rep* 2018; **8**: 74 [PMID: 29311617 DOI: 10.1038/s41598-017-18259-0]
- 61 **Primec M**, Klemenak M, Di Gioia D, Aloisio I, Bozzi Cionci N, Quagliariello A, Gorenjak M, Mičetić-Turk D, Langerholc T. Clinical intervention using *Bifidobacterium* strains in celiac disease children reveals novel microbial modulators of TNF- α and short-chain fatty acids. *Clin Nutr* 2019; **38**: 1373-1381 [PMID: 29960810 DOI: 10.1016/j.clnu.2018.06.931]
- 62 **Tuncil YE**, Thakkar RD, Marcia ADR, Hamaker BR, Lindemann SR. Divergent short-chain fatty acid production and succession of colonic microbiota arise in fermentation of variously-sized wheat bran fractions. *Sci Rep* 2018; **8**: 16655 [PMID: 30413754 DOI: 10.1038/s41598-018-34912-8]
- 63 **Sun N**, Wang L, Tong L, Zhou X, Liu L, Sun Y, Zhou S. Comparison of Structural and Functional Characterizations of Arabinoxylans from Different Wheat Processing Varieties. *Plant Foods Hum Nutr* 2019; **74**: 376-382 [PMID: 31222476 DOI: 10.1007/s11130-019-00734-w]
- 64 **Kaiko GE**, Ryu SH, Koues OI, Collins PL, Solnica-Krezel L, Pearce EJ, Pearce EL, Oltz EM, Stappenbeck TS. The Colonic Crypt Protects Stem Cells from Microbiota-Derived Metabolites. *Cell* 2016; **165**: 1708-1720 [PMID: 27264604 DOI: 10.1016/j.cell.2016.05.018]
- 65 **Zhou B**, Yuan Y, Zhang S, Guo C, Li X, Li G, Xiong W, Zeng Z. Intestinal Flora and Disease Mutually Shape the Regional Immune System in the Intestinal Tract. *Front Immunol* 2020; **11**: 575 [PMID: 32318067 DOI: 10.3389/fimmu.2020.00575]
- 66 **Kim M**, Qie Y, Park J, Kim CH. Gut Microbial Metabolites Fuel Host Antibody Responses. *Cell Host Microbe* 2016; **20**: 202-214 [PMID: 27476413 DOI: 10.1016/j.chom.2016.07.001]
- 67 **Al Nabhani Z**, Dulauroy S, Marques R, Cousu C, Al Bounny S, Déjardin F, Sparwasser T, Bérard M, Cerf-Bensussan N, Eberl G. A Weaning Reaction to Microbiota Is Required for Resistance to Immunopathologies in the Adult. *Immunity* 2019; **50**: 1276-1288.e5 [PMID: 30902637 DOI: 10.1016/j.immuni.2019.02.014]
- 68 **Machiels K**, Joossens M, Sabino J, De Preter V, Arijis I, Eeckhaut V, Ballet V, Claes K, Van Immerseel F, Verbeke K, Ferrante M, Verhaegen J, Rutgeerts P, Vermeire S. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut* 2014; **63**: 1275-1283 [PMID: 24021287 DOI: 10.1136/gutjnl-2013-304833]
- 69 **Laserna-Mendieta EJ**, Clooney AG, Carretero-Gomez JF, Moran C, Sheehan D, Nolan JA, Hill C, Gahan CGM, Joyce SA, Shanahan F, Claesson MJ. Determinants of Reduced Genetic Capacity for Butyrate Synthesis by the Gut Microbiome in Crohn's Disease and Ulcerative Colitis. *J Crohns Colitis* 2018; **12**: 204-216 [PMID: 29373727 DOI: 10.1093/ecco-jcc/jjx137]
- 70 **Wang Y**, Leong LEX, Keating RL, Kanno T, Abell GCJ, Mobegi FM, Choo JM, Wesselingh SL, Mason AJ, Burr LD, Rogers GB. Opportunistic bacteria confer the ability to ferment prebiotic starch in the adult cystic fibrosis gut. *Gut Microbes* 2019; **10**: 367-381 [PMID: 30359203 DOI: 10.1080/19490976.2018.1534512]
- 71 **Hove H**, Mortensen PB. Influence of intestinal inflammation (IBD) and small and large bowel length on fecal short-chain fatty acids and lactate. *Dig Dis Sci* 1995; **40**: 1372-1380 [PMID: 7781463 DOI: 10.1007/BF02065554]
- 72 **Pekmez CT**, Dragsted LO, Brahe LK. Gut microbiota alterations and dietary modulation in childhood malnutrition - The role of short chain fatty acids. *Clin Nutr* 2019; **38**: 615-630 [PMID: 29496274 DOI: 10.1016/j.clnu.2018.02.014]
- 73 **Wang S**, Dong W, Liu L, Xu M, Wang Y, Liu T, Zhang Y, Wang B, Cao H. Interplay between bile acids and the gut microbiota promotes intestinal carcinogenesis. *Mol Carcinog* 2019; **58**: 1155-1167 [PMID: 30828892 DOI: 10.1002/mc.22999]
- 74 **Morrison DJ**, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* 2016; **7**: 189-200 [PMID: 26963409 DOI: 10.1080/19490976.2015.1134082]
- 75 **Xiao H**, Kang S. The Role of the Gut Microbiome in Energy Balance With a Focus on the Gut-Adipose Tissue Axis. *Front Genet* 2020; **11**: 297 [PMID: 32318095 DOI: 10.3389/fgene.2020.00297]
- 76 **Canli PD**, Van Hul M, Lefort C, Depommier C, Rastelli M, Everard A. Microbial regulation of organismal energy homeostasis. *Nat Metab* 2019; **1**: 34-46 [PMID: 32694818 DOI: 10.1038/s42255-018-0017-4]
- 77 **Schmalle V**, Lorentz A. Role of the microbiota in circadian rhythms of the host. *Chronobiol Int* 2020; **37**: 301-310 [PMID: 32050806 DOI: 10.1080/07420528.2020.1726374]
- 78 **Quévrain E**, Maubert MA, Michon C, Chain F, Marquant R, Tailhades J, Miquel S, Carlier L, Bermúdez-Humarán LG,

- Pigneur B, Lequin O, Kharrat P, Thomas G, Rainteau D, Aubry C, Breyner N, Afonso C, Lavielle S, Grill JP, Chassaing G, Chatel JM, Trugnan G, Xavier R, Langella P, Sokol H, Seksik P. Identification of an anti-inflammatory protein from *Faecalibacterium prausnitzii*, a commensal bacterium deficient in Crohn's disease. *Gut* 2016; **65**: 415-425 [PMID: 26045134 DOI: 10.1136/gutjnl-2014-307649]
- 79 Barra M, Danino T, Garrido D. Engineered Probiotics for Detection and Treatment of Inflammatory Intestinal Diseases. *Front Bioeng Biotechnol* 2020; **8**: 265 [PMID: 32296696 DOI: 10.3389/fbioe.2020.00265]
- 80 Tully DC, Rucker PV, Chianelli D, Williams J, Vidal A, Alper PB, Mutnick D, Bursulaya B, Schmeits J, Wu X, Bao D, Zoll J, Kim Y, Groessl T, McNamara P, Seidel HM, Molteni V, Liu B, Phimister A, Joseph SB, Laffitte B. Discovery of Tropifexor (LJN452), a Highly Potent Non-bile Acid FXR Agonist for the Treatment of Cholestatic Liver Diseases and Nonalcoholic Steatohepatitis (NASH). *J Med Chem* 2017; **60**: 9960-9973 [PMID: 29148806 DOI: 10.1021/acs.jmedchem.7b00907]
- 81 Deutschmann K, Reich M, Klindt C, Dröge C, Spomer L, Häussinger D, Keitel V. Bile acid receptors in the biliary tree: TGR5 in physiology and disease. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 1319-1325 [PMID: 28844960 DOI: 10.1016/j.bbadis.2017.08.021]
- 82 Joyce SA, Gahan CG. Disease-Associated Changes in Bile Acid Profiles and Links to Altered Gut Microbiota. *Dig Dis* 2017; **35**: 169-177 [PMID: 28249284 DOI: 10.1159/000450907]
- 83 Vaughn BP, Kaiser T, Staley C, Hamilton MJ, Reich J, Graiziger C, Singroy S, Kabage AJ, Sadowsky MJ, Khoruts A. A pilot study of fecal bile acid and microbiota profiles in inflammatory bowel disease and primary sclerosing cholangitis. *Clin Exp Gastroenterol* 2019; **12**: 9-19 [PMID: 30666146 DOI: 10.2147/CEG.S186097]
- 84 Darnaud M, Dos Santos A, Gonzalez P, Augui S, Lacoste C, Desterke C, De Hertogh G, Valentino E, Braun E, Zheng J, Boisgard R, Neut C, Dubuquoy L, Chiappini F, Samuel D, Lepage P, Guerrieri F, Doré J, Bréchet C, Moniaux N, Faivre J. Enteric Delivery of Regenerating Family Member 3 alpha Alters the Intestinal Microbiota and Controls Inflammation in Mice With Colitis. *Gastroenterology* 2018; **154**: 1009-1023.e14 [PMID: 29133078 DOI: 10.1053/j.gastro.2017.11.003]
- 85 Rau M, Stieger B, Monte MJ, Schmitt J, Jahn D, Frey-Wagner I, Raselli T, Marin JJ, Müllhaupt B, Rogler G, Geier A. Alterations in Enterohepatic Fgf15 Signaling and Changes in Bile Acid Composition Depend on Localization of Murine Intestinal Inflammation. *Inflamm Bowel Dis* 2016; **22**: 2382-2389 [PMID: 27580383 DOI: 10.1097/MIB.0000000000000879]
- 86 Xu M, Cen M, Shen Y, Zhu Y, Cheng F, Tang L, Hu W, Dai N. Deoxycholic Acid-Induced Gut Dysbiosis Disrupts Bile Acid Enterohepatic Circulation and Promotes Intestinal Inflammation. *Dig Dis Sci* 2021; **66**: 568-576 [PMID: 32198567 DOI: 10.1007/s10620-020-06208-3]
- 87 Ticho AL, Malhotra P, Dudeja PK, Gill RK, Alrefai WA. Bile Acid Receptors and Gastrointestinal Functions. *Liver Res* 2019; **3**: 31-39 [PMID: 32368358 DOI: 10.1016/j.livres.2019.01.001]
- 88 Guard BC, Suchodolski JS. HORSE SPECIES SYMPOSIUM: Canine intestinal microbiology and metagenomics: From phylogeny to function. *J Anim Sci* 2016; **94**: 2247-2261 [PMID: 27285902 DOI: 10.2527/jas.2015-0029]
- 89 Song X, Sun X, Oh SF, Wu M, Zhang Y, Zheng W, Geva-Zatorsky N, Jupp R, Mathis D, Benoist C, Kasper DL. Microbial bile acid metabolites modulate gut ROR γ ⁺ regulatory T cell homeostasis. *Nature* 2020; **577**: 410-415 [PMID: 31875848 DOI: 10.1038/s41586-019-1865-0]
- 90 Guo J, Shao J, Yang Y, Niu X, Liao J, Zhao Q, Wang D, Li S, Hu J. Gut Microbiota in Patients with Polycystic Ovary Syndrome: a Systematic Review. *Reprod Sci* 2022; **29**: 69-83 [PMID: 33409871 DOI: 10.1007/s43032-020-00430-0]
- 91 Van den Bossche L, Borsboom D, Devriese S, Van Welden S, Holvoet T, Devisscher L, Hindryckx P, De Vos M, Laukens D. Tauroursodeoxycholic acid protects bile acid homeostasis under inflammatory conditions and dampens Crohn's disease-like ileitis. *Lab Invest* 2017; **97**: 519-529 [PMID: 28165466 DOI: 10.1038/labinvest.2017.6]
- 92 Franzosa EA, Sirota-Madi A, Avila-Pacheco J, Fornelos N, Haiser HJ, Reinker S, Vatanen T, Hall AB, Mallick H, McIver LJ, Sauk JS, Wilson RG, Stevens BW, Scott JM, Pierce K, Deik AA, Bullock K, Imhann F, Porter JA, Zhernakova A, Fu J, Weersma RK, Wijmenga C, Clish CB, Vlamakis H, Huttenhower C, Xavier RJ. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat Microbiol* 2019; **4**: 293-305 [PMID: 30531976 DOI: 10.1038/s41564-018-0306-4]
- 93 Torres J, Palmela C, Brito H, Bao X, Ruiqi H, Moura-Santos P, Pereira da Silva J, Oliveira A, Vieira C, Perez K, Itzkowitz SH, Colombel JF, Humbert L, Rainteau D, Cravo M, Rodrigues CM, Hu J. The gut microbiota, bile acids and their correlation in primary sclerosing cholangitis associated with inflammatory bowel disease. *United European Gastroenterol J* 2018; **6**: 112-122 [PMID: 29435321 DOI: 10.1177/2050640617708953]
- 94 Lucas López R, Grande Burgos MJ, Gálvez A, Pérez Pulido R. The human gastrointestinal tract and oral microbiota in inflammatory bowel disease: a state of the science review. *APMIS* 2017; **125**: 3-10 [PMID: 27704622 DOI: 10.1111/apm.12609]
- 95 Joyce SA, MacSharry J, Casey PG, Kinsella M, Murphy EF, Shanahan F, Hill C, Gahan CG. Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. *Proc Natl Acad Sci U S A* 2014; **111**: 7421-7426 [PMID: 24799697 DOI: 10.1073/pnas.1323599111]
- 96 Lorenzo-Zúñiga V, Bartolí R, Planas R, Hofmann AF, Viñado B, Hagey LR, Hernández JM, Mañé J, Alvarez MA, Ausina V, Gassull MA. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. *Hepatology* 2003; **37**: 551-557 [PMID: 12601352 DOI: 10.1053/jhep.2003.50116]
- 97 Hajjagha MN, Taghizadeh S, Asgharzadeh M, Dao S, Ganbarov K, Köse Ş, Kafıl HS. Gut Microbiota and Human Body Interactions; Its Impact on Health: A Review. *Curr Pharm Biotechnol* 2022; **23**: 4-14 [PMID: 33397232 DOI: 10.2174/1389201022666210104115836]
- 98 Van den Bossche L, Hindryckx P, Devisscher L, Devriese S, Van Welden S, Holvoet T, Vilchez-Vargas R, Vital M, Pieper DH, Vanden Bussche J, Vanhaecke L, Van de Wiele T, De Vos M, Laukens D. Ursodeoxycholic Acid and Its Taurine- or Glycine-Conjugated Species Reduce Colitogenic Dysbiosis and Equally Suppress Experimental Colitis in Mice. *Appl Environ Microbiol* 2017; **83** [PMID: 28115375 DOI: 10.1128/AEM.02766-16]
- 99 Baars A, Oosting A, Knol J, Garssen J, van Bergenhenegouwen J. The Gut Microbiota as a Therapeutic Target in IBD and Metabolic Disease: A Role for the Bile Acid Receptors FXR and TGR5. *Microorganisms* 2015; **3**: 641-666 [PMID: 26045134 DOI: 10.1136/gutjnl-2014-307649]

- 27682110 DOI: [10.3390/microorganisms3040641](https://doi.org/10.3390/microorganisms3040641)]
- 100 **Milshcheyn A**, Colosimo DA, Brady SF. Accessing Bioactive Natural Products from the Human Microbiome. *Cell Host Microbe* 2018; **23**: 725-736 [PMID: [29902438](https://pubmed.ncbi.nlm.nih.gov/29902438/) DOI: [10.1016/j.chom.2018.05.013](https://doi.org/10.1016/j.chom.2018.05.013)]
 - 101 **Martin R**, Miquel S, Benevides L, Bridonneau C, Robert V, Hudault S, Chain F, Berteau O, Azevedo V, Chatel JM, Sokol H, Bermúdez-Humarán LG, Thomas M, Langella P. Functional Characterization of Novel *Faecalibacterium prausnitzii* Strains Isolated from Healthy Volunteers: A Step Forward in the Use of *F. prausnitzii* as a Next-Generation Probiotic. *Front Microbiol* 2017; **8**: 1226 [PMID: [28713353](https://pubmed.ncbi.nlm.nih.gov/28713353/) DOI: [10.3389/fmicb.2017.01226](https://doi.org/10.3389/fmicb.2017.01226)]
 - 102 **van Beurden YH**, de Groot PF, van Nood E, Nieuwdorp M, Keller JJ, Goorhuis A. Complications, effectiveness, and long term follow-up of fecal microbiota transfer by nasoduodenal tube for treatment of recurrent *Clostridium difficile* infection. *United European Gastroenterol J* 2017; **5**: 868-879 [PMID: [29026601](https://pubmed.ncbi.nlm.nih.gov/29026601/) DOI: [10.1177/2050640616678099](https://doi.org/10.1177/2050640616678099)]
 - 103 **Chang CJ**, Lin TL, Tsai YL, Wu TR, Lai WF, Lu CC, Lai HC. Next generation probiotics in disease amelioration. *J Food Drug Anal* 2019; **27**: 615-622 [PMID: [31324278](https://pubmed.ncbi.nlm.nih.gov/31324278/) DOI: [10.1016/j.jfda.2018.12.011](https://doi.org/10.1016/j.jfda.2018.12.011)]
 - 104 **Ganesan K**, Chung SK, Vanamala J, Xu B. Causal Relationship between Diet-Induced Gut Microbiota Changes and Diabetes: A Novel Strategy to Transplant Faecalibacterium prausnitzii in Preventing Diabetes. *Int J Mol Sci* 2018; **19** [PMID: [30467295](https://pubmed.ncbi.nlm.nih.gov/30467295/) DOI: [10.3390/ijms19123720](https://doi.org/10.3390/ijms19123720)]
 - 105 **Rossi O**, van Berkel LA, Chain F, Tanweer Khan M, Taverne N, Sokol H, Duncan SH, Flint HJ, Harmsen HJ, Langella P, Samsom JN, Wells JM. Faecalibacterium prausnitzii A2-165 has a high capacity to induce IL-10 in human and murine dendritic cells and modulates T cell responses. *Sci Rep* 2016; **6**: 18507 [PMID: [26725514](https://pubmed.ncbi.nlm.nih.gov/26725514/) DOI: [10.1038/srep18507](https://doi.org/10.1038/srep18507)]
 - 106 **Michonneau D**, Latis E, Curis E, Dubouchet L, Ramamoorthy S, Ingram B, de Latour RP, Robin M, de Fontbrune FS, Chevret S, Rogge L, Socié G. Metabolomics analysis of human acute graft-versus-host disease reveals changes in host and microbiota-derived metabolites. *Nat Commun* 2019; **10**: 5695 [PMID: [31836702](https://pubmed.ncbi.nlm.nih.gov/31836702/) DOI: [10.1038/s41467-019-13498-3](https://doi.org/10.1038/s41467-019-13498-3)]
 - 107 **Amedei A**, Morbidelli L. Circulating Metabolites Originating from Gut Microbiota Control Endothelial Cell Function. *Molecules* 2019; **24** [PMID: [31694161](https://pubmed.ncbi.nlm.nih.gov/31694161/) DOI: [10.3390/molecules24213992](https://doi.org/10.3390/molecules24213992)]
 - 108 **Ji Y**, Gao Y, Chen H, Yin Y, Zhang W. Indole-3-Acetic Acid Alleviates Nonalcoholic Fatty Liver Disease in Mice via Attenuation of Hepatic Lipogenesis, and Oxidative and Inflammatory Stress. *Nutrients* 2019; **11** [PMID: [31484323](https://pubmed.ncbi.nlm.nih.gov/31484323/) DOI: [10.3390/nu11092062](https://doi.org/10.3390/nu11092062)]
 - 109 **Armand L**, Andriamihaja M, Gellenoncourt S, Bitane V, Lan A, Blachier F. In vitro impact of amino acid-derived bacterial metabolites on colonocyte mitochondrial activity, oxidative stress response and DNA integrity. *Biochim Biophys Acta Gen Subj* 2019; **1863**: 1292-1301 [PMID: [31034912](https://pubmed.ncbi.nlm.nih.gov/31034912/) DOI: [10.1016/j.bbagen.2019.04.018](https://doi.org/10.1016/j.bbagen.2019.04.018)]
 - 110 **Zhang S**, Zhao Y, Ohland C, Jobin C, Sang S. Microbiota facilitates the formation of the aminated metabolite of green tea polyphenol (-)-epigallocatechin-3-gallate which trap deleterious reactive endogenous metabolites. *Free Radic Biol Med* 2019; **131**: 332-344 [PMID: [30578921](https://pubmed.ncbi.nlm.nih.gov/30578921/) DOI: [10.1016/j.freeradbiomed.2018.12.023](https://doi.org/10.1016/j.freeradbiomed.2018.12.023)]
 - 111 **Álvarez-Cillerós D**, Ramos S, Goya L, Martín MÁ. Colonic metabolites from flavanols stimulate nitric oxide production in human endothelial cells and protect against oxidative stress-induced toxicity and endothelial dysfunction. *Food Chem Toxicol* 2018; **115**: 88-97 [PMID: [29530637](https://pubmed.ncbi.nlm.nih.gov/29530637/) DOI: [10.1016/j.fct.2018.03.006](https://doi.org/10.1016/j.fct.2018.03.006)]
 - 112 **Sartor RB**, Wu GD. Roles for Intestinal Bacteria, Viruses, and Fungi in Pathogenesis of Inflammatory Bowel Diseases and Therapeutic Approaches. *Gastroenterology* 2017; **152**: 327-339.e4 [PMID: [27769810](https://pubmed.ncbi.nlm.nih.gov/27769810/) DOI: [10.1053/j.gastro.2016.10.012](https://doi.org/10.1053/j.gastro.2016.10.012)]
 - 113 **Li KY**, Wang JL, Wei JP, Gao SY, Zhang YY, Wang LT, Liu G. Fecal microbiota in pouchitis and ulcerative colitis. *World J Gastroenterol* 2016; **22**: 8929-8939 [PMID: [27833384](https://pubmed.ncbi.nlm.nih.gov/27833384/) DOI: [10.3748/wjg.v22.i40.8929](https://doi.org/10.3748/wjg.v22.i40.8929)]
 - 114 **De Preter Y**, Machiels K, Joossens M, Arijis I, Matthys C, Vermeire S, Rutgeerts P, Verbeke K. Faecal metabolite profiling identifies medium-chain fatty acids as discriminating compounds in IBD. *Gut* 2015; **64**: 447-458 [PMID: [24811995](https://pubmed.ncbi.nlm.nih.gov/24811995/) DOI: [10.1136/gutjnl-2013-306423](https://doi.org/10.1136/gutjnl-2013-306423)]
 - 115 **Pierre JF**, Hinterleitner R, Bouziat R, Hubert NA, Leone V, Miyoshi J, Jabri B, Chang EB. Dietary antioxidant micronutrients alter mucosal inflammatory risk in a murine model of genetic and microbial susceptibility. *J Nutr Biochem* 2018; **54**: 95-104 [PMID: [29331497](https://pubmed.ncbi.nlm.nih.gov/29331497/) DOI: [10.1016/j.jnutbio.2017.12.002](https://doi.org/10.1016/j.jnutbio.2017.12.002)]
 - 116 **Landy J**, Walker AW, Li JV, Al-Hassi HO, Ronde E, English NR, Mann ER, Bernardo D, McLaughlin SD, Parkhill J, Ciclitira PJ, Clark SK, Knight SC, Hart AL. Variable alterations of the microbiota, without metabolic or immunological change, following faecal microbiota transplantation in patients with chronic pouchitis. *Sci Rep* 2015; **5**: 12955 [PMID: [26264409](https://pubmed.ncbi.nlm.nih.gov/26264409/) DOI: [10.1038/srep12955](https://doi.org/10.1038/srep12955)]
 - 117 **Agus A**, Planchais J, Sokol H. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host Microbe* 2018; **23**: 716-724 [PMID: [29902437](https://pubmed.ncbi.nlm.nih.gov/29902437/) DOI: [10.1016/j.chom.2018.05.003](https://doi.org/10.1016/j.chom.2018.05.003)]
 - 118 **Lin L**, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. *BMC Immunol* 2017; **18**: 2 [PMID: [28061847](https://pubmed.ncbi.nlm.nih.gov/28061847/) DOI: [10.1186/s12865-016-0187-3](https://doi.org/10.1186/s12865-016-0187-3)]
 - 119 **Little R**, Wine E, Kamath BM, Griffiths AM, Ricciuto A. Gut microbiome in primary sclerosing cholangitis: A review. *World J Gastroenterol* 2020; **26**: 2768-2780 [PMID: [32550753](https://pubmed.ncbi.nlm.nih.gov/32550753/) DOI: [10.3748/wjg.v26.i21.2768](https://doi.org/10.3748/wjg.v26.i21.2768)]
 - 120 **Gasaly N**, de Vos P, Hermoso MA. Impact of Bacterial Metabolites on Gut Barrier Function and Host Immunity: A Focus on Bacterial Metabolism and Its Relevance for Intestinal Inflammation. *Front Immunol* 2021; **12**: 658354 [PMID: [34122415](https://pubmed.ncbi.nlm.nih.gov/34122415/) DOI: [10.3389/fimmu.2021.658354](https://doi.org/10.3389/fimmu.2021.658354)]
 - 121 **Yang C**, Zhao Y, Im S, Nakatsu C, Jones-Hall Y, Jiang Q. Vitamin E delta-tocotrienol and metabolite 13'-carboxychromanol inhibit colitis-associated colon tumorigenesis and modulate gut microbiota in mice. *J Nutr Biochem* 2021; **89**: 108567 [PMID: [33347911](https://pubmed.ncbi.nlm.nih.gov/33347911/) DOI: [10.1016/j.jnutbio.2020.108567](https://doi.org/10.1016/j.jnutbio.2020.108567)]
 - 122 **Bischoff SC**, Kaden-Volynets V, Filipe Rosa L, Guseva D, Seethaler B. Regulation of the gut barrier by carbohydrates from diet - Underlying mechanisms and possible clinical implications. *Int J Med Microbiol* 2021; **311**: 151499 [PMID: [33864957](https://pubmed.ncbi.nlm.nih.gov/33864957/) DOI: [10.1016/j.ijmm.2021.151499](https://doi.org/10.1016/j.ijmm.2021.151499)]
 - 123 **Shi J**, Du P, Xie Q, Wang N, Li H, Smith EE, Li C, Liu F, Huo G, Li B. Protective effects of tryptophan-catabolizing *Lactobacillus plantarum* KLDS 1.0386 against dextran sodium sulfate-induced colitis in mice. *Food Funct* 2020; **11**: 10736-10747 [PMID: [33231244](https://pubmed.ncbi.nlm.nih.gov/33231244/) DOI: [10.1039/d0fo02622k](https://doi.org/10.1039/d0fo02622k)]

- 124 **Bunt DV**, Minnaard AJ, El Aidy S. Potential Modulatory Microbiome Therapies for Prevention or Treatment of Inflammatory Bowel Diseases. *Pharmaceuticals (Basel)* 2021; **14** [PMID: [34073220](#) DOI: [10.3390/ph14060506](#)]
- 125 **Pascoal LB**, Rodrigues PB, Genaro LM, Gomes ABDSP, Toledo-Teixeira DA, Parise PL, Bispo-Dos-Santos K, Simeoni CL, Guimarães PV, Buscaratti LI, Elston JGA, Marques-Souza H, Martins-de-Souza D, Ayrizono MLS, Velloso LA, Proenca-Modena JL, Moraes-Vieira PMM, Mori MAS, Farias AS, Vinolo MAR, Leal RF. Microbiota-derived short-chain fatty acids do not interfere with SARS-CoV-2 infection of human colonic samples. *Gut Microbes* 2021; **13**: 1-9 [PMID: [33550892](#) DOI: [10.1080/19490976.2021.1874740](#)]
- 126 **Singhal S**, Rani V. Study to Explore Plant-Derived Trimethylamine Lyase Enzyme Inhibitors to Address Gut Dysbiosis. *Appl Biochem Biotechnol* 2022; **194**: 99-123 [PMID: [34822060](#) DOI: [10.1007/s12010-021-03747-x](#)]
- 127 **Li B**, Zhang H, Shi L, Li R, Luo Y, Deng Y, Li S, Liu Z. *Saccharomyces boulardii* alleviates DSS-induced intestinal barrier dysfunction and inflammation in humanized mice. *Food Funct* 2022; **13**: 102-112 [PMID: [34878454](#) DOI: [10.1039/d1fo02752b](#)]
- 128 **Komatsu Y**, Shimizu Y, Yamano M, Kikuchi M, Nakamura K, Ayabe T, Aizawa T. Disease progression-associated alterations in fecal metabolites in SAMP1/YitFc mice, a Crohn's disease model. *Metabolomics* 2020; **16**: 48 [PMID: [32274593](#) DOI: [10.1007/s11306-020-01671-5](#)]
- 129 **Melhem H**, Kaya B, Ayata CK, Hruz P, Niess JH. Metabolite-Sensing G Protein-Coupled Receptors Connect the Diet-Microbiota-Metabolites Axis to Inflammatory Bowel Disease. *Cells* 2019; **8** [PMID: [31091682](#) DOI: [10.3390/cells8050450](#)]
- 130 **Ong HS**, Yim HCH. Microbial Factors in Inflammatory Diseases and Cancers. *Adv Exp Med Biol* 2017; **1024**: 153-174 [PMID: [28921469](#) DOI: [10.1007/978-981-10-5987-2_7](#)]
- 131 **Yang W**, Cong Y. Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cell Mol Immunol* 2021; **18**: 866-877 [PMID: [33707689](#) DOI: [10.1038/s41423-021-00661-4](#)]
- 132 **Nishida A**, Nishino K, Sakai K, Owaki Y, Noda Y, Imaeda H. Can control of gut microbiota be a future therapeutic option for inflammatory bowel disease? *World J Gastroenterol* 2021; **27**: 3317-3326 [PMID: [34163114](#) DOI: [10.3748/wjg.v27.i23.3317](#)]
- 133 **Xiu W**, Chen Q, Wang Z, Wang J, Zhou Z. Microbiota-derived short chain fatty acid promotion of Amphiregulin expression by dendritic cells is regulated by GPR43 and Blimp-1. *Biochem Biophys Res Commun* 2020; **533**: 282-288 [PMID: [32958255](#) DOI: [10.1016/j.bbrc.2020.09.027](#)]
- 134 **Qiu X**, Macchietto MG, Liu X, Lu Y, Ma Y, Guo H, Saqui-Salces M, Bernlohr DA, Chen C, Shen S, Chen X. Identification of gut microbiota and microbial metabolites regulated by an antimicrobial peptide lipocalin 2 in high fat diet-induced obesity. *Int J Obes (Lond)* 2021; **45**: 143-154 [PMID: [33214705](#) DOI: [10.1038/s41366-020-00712-2](#)]
- 135 **Markandey M**, Bajaj A, Ilott NE, Kedia S, Travis S, Powrie F, Ahuja V. Gut microbiota: sculptors of the intestinal stem cell niche in health and inflammatory bowel disease. *Gut Microbes* 2021; **13**: 1990827 [PMID: [34747326](#) DOI: [10.1080/19490976.2021.1990827](#)]
- 136 **DeLuca JA**, Allred KF, Menon R, Riordan R, Weeks BR, Jayaraman A, Allred CD. Bisphenol-A alters microbiota metabolites derived from aromatic amino acids and worsens disease activity during colitis. *Exp Biol Med (Maywood)* 2018; **243**: 864-875 [PMID: [29874946](#) DOI: [10.1177/1535370218782139](#)]
- 137 **Ward JBJ**, Lajczak NK, Kelly OB, O'Dwyer AM, Giddam AK, Ni Gabhann J, Franco P, Tambuwala MM, Jefferies CA, Keely S, Roda A, Keely SJ. Ursodeoxycholic acid and lithocholic acid exert anti-inflammatory actions in the colon. *Am J Physiol Gastrointest Liver Physiol* 2017; **312**: G550-G558 [PMID: [28360029](#) DOI: [10.1152/ajpgi.00256.2016](#)]
- 138 **Verdugo-Meza A**, Ye J, Dadlani H, Ghosh S, Gibson DL. Connecting the Dots Between Inflammatory Bowel Disease and Metabolic Syndrome: A Focus on Gut-Derived Metabolites. *Nutrients* 2020; **12** [PMID: [32429195](#) DOI: [10.3390/nu12051434](#)]
- 139 **Song D**, Lai L, Ran Z. Metabolic Regulation of Group 3 Innate Lymphoid Cells and Their Role in Inflammatory Bowel Disease. *Front Immunol* 2020; **11**: 580467 [PMID: [33193381](#) DOI: [10.3389/fimmu.2020.580467](#)]
- 140 **Wojciech L**, Tan KSW, Gascoigne NRJ. Taming the Sentinels: Microbiome-Derived Metabolites and Polarization of T Cells. *Int J Mol Sci* 2020; **21** [PMID: [33086747](#) DOI: [10.3390/ijms21207740](#)]
- 141 **Mogilnicka I**, Ufnal M. Gut Mycobiota and Fungal Metabolites in Human Homeostasis. *Curr Drug Targets* 2019; **20**: 232-240 [PMID: [30047327](#) DOI: [10.2174/1389450119666180724125020](#)]
- 142 **Loo YT**, Howell K, Chan M, Zhang P, Ng K. Modulation of the human gut microbiota by phenolics and phenolic fiber-rich foods. *Compr Rev Food Sci Food Saf* 2020; **19**: 1268-1298 [PMID: [33337077](#) DOI: [10.1111/1541-4337.12563](#)]
- 143 **Banfi D**, Moro E, Bosi A, Bistoletti M, Cerantola S, Crema F, Maggi F, Giron MC, Giaroni C, Baj A. Impact of Microbial Metabolites on Microbiota-Gut-Brain Axis in Inflammatory Bowel Disease. *Int J Mol Sci* 2021; **22** [PMID: [33562721](#) DOI: [10.3390/ijms22041623](#)]
- 144 **Coman V**, Vodnar DC. Gut microbiota and old age: Modulating factors and interventions for healthy longevity. *Exp Gerontol* 2020; **141**: 111095 [PMID: [32979504](#) DOI: [10.1016/j.exger.2020.111095](#)]
- 145 **Zeng SL**, Li SZ, Xiao PT, Cai YY, Chu C, Chen BZ, Li P, Li J, Liu EH. Citrus polymethoxyflavones attenuate metabolic syndrome by regulating gut microbiome and amino acid metabolism. *Sci Adv* 2020; **6**: eaax6208 [PMID: [31922003](#) DOI: [10.1126/sciadv.aax6208](#)]
- 146 **Kc D**, Sumner R, Lippmann S. Gut microbiota and health. *Postgrad Med* 2020; **132**: 274 [PMID: [31566046](#) DOI: [10.1080/00325481.2019.1662711](#)]
- 147 **Yu F**, Jiang R, Han W, Zhan G, Xu X, Jiang X, Wang L, Xiang S, Zhou Q, Liu C, Zhu B, Hua F, Yang C. Gut microbiota transplantation from db/db mice induces diabetes-like phenotypes and alterations in Hippo signaling in pseudo germ-free mice. *Aging (Albany NY)* 2020; **12**: 24156-24167 [PMID: [33223509](#) DOI: [10.18632/aging.104101](#)]
- 148 **Woldeamlak B**, Yirdaw K, Biadgo B. Role of Gut Microbiota in Type 2 Diabetes Mellitus and Its Complications: Novel Insights and Potential Intervention Strategies. *Korean J Gastroenterol* 2019; **74**: 314-320 [PMID: [31870137](#) DOI: [10.4166/kjg.2019.74.6.314](#)]
- 149 **Napolitano M**, Covasa M. Microbiota Transplant in the Treatment of Obesity and Diabetes: Current and Future Perspectives. *Front Microbiol* 2020; **11**: 590370 [PMID: [33304339](#) DOI: [10.3389/fmicb.2020.590370](#)]

- 150 **Rasmussen TS**, Koefoed AK, Jakobsen RR, Deng L, Castro-Mejía JL, Brunse A, Neve H, Vogensen FK, Nielsen DS. Bacteriophage-mediated manipulation of the gut microbiome - promises and presents limitations. *FEMS Microbiol Rev* 2020; **44**: 507-521 [PMID: [32495834](#) DOI: [10.1093/femsre/fuaa020](#)]
- 151 **Barba C**, Soulage CO, Caggiano G, Glorieux G, Fouque D, Koppe L. Effects of Fecal Microbiota Transplantation on Composition in Mice with CKD. *Toxins (Basel)* 2020; **12** [PMID: [33255454](#) DOI: [10.3390/toxins12120741](#)]
- 152 **Gilbert B**, Schrenzel J. [Fecal microbiota transplantation : current status and prospects]. *Rev Med Suisse* 2019; **15**: 976-983 [PMID: [31066530](#)]
- 153 **Bajaj JS**, Kassam Z, Fagan A, Gavis EA, Liu E, Cox JJ, Kheradman R, Heuman D, Wang J, Gurry T, Williams R, Sikaroodi M, Fuchs M, Alm E, John B, Thacker LR, Riva A, Smith M, Taylor-Robinson SD, Gillevet PM. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* 2017; **66**: 1727-1738 [PMID: [28586116](#) DOI: [10.1002/hep.29306](#)]
- 154 **Simpson CA**, Diaz-Arteche C, Eliby D, Schwartz OS, Simmons JG, Cowan CSM. The gut microbiota in anxiety and depression - A systematic review. *Clin Psychol Rev* 2021; **83**: 101943 [PMID: [33271426](#) DOI: [10.1016/j.cpr.2020.101943](#)]
- 155 **Merra G**, Noce A, Marrone G, Cintoni M, Tarsitano MG, Capacci A, De Lorenzo A. Influence of Mediterranean Diet on Human Gut Microbiota. *Nutrients* 2020; **13** [PMID: [33375042](#) DOI: [10.3390/nu13010007](#)]
- 156 **Konjevod M**, Nikolac Perkovic M, Sáiz J, Svob Strac D, Barbas C, Rojo D. Metabolomics analysis of microbiota-gut-brain axis in neurodegenerative and psychiatric diseases. *J Pharm Biomed Anal* 2021; **194**: 113681 [PMID: [33279302](#) DOI: [10.1016/j.jpba.2020.113681](#)]
- 157 **Duttaroy AK**. Role of Gut Microbiota and Their Metabolites on Atherosclerosis, Hypertension and Human Blood Platelet Function: A Review. *Nutrients* 2021; **13** [PMID: [33401598](#) DOI: [10.3390/nu13010144](#)]
- 158 **Fu Y**, Wang Y, Gao H, Li D, Jiang R, Ge L, Tong C, Xu K. Associations among Dietary Omega-3 Polyunsaturated Fatty Acids, the Gut Microbiota, and Intestinal Immunity. *Mediators Inflamm* 2021; **2021**: 8879227 [PMID: [33488295](#) DOI: [10.1155/2021/8879227](#)]
- 159 **Wan MLY**, Co VA, El-Nezami H. Dietary polyphenol impact on gut health and microbiota. *Crit Rev Food Sci Nutr* 2021; **61**: 690-711 [PMID: [32208932](#) DOI: [10.1080/10408398.2020.1744512](#)]
- 160 **Settanni CR**, Bibbò S, Ianiro G, Rinninella E, Cintoni M, Mele MC, Cammarota G, Gasbarrini A. Gastrointestinal involvement of autism spectrum disorder: focus on gut microbiota. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 599-622 [PMID: [33356668](#) DOI: [10.1080/17474124.2021.1869938](#)]
- 161 **Badgeley A**, Anwar H, Modi K, Murphy P, Lakshmikuttyamma A. Effect of probiotics and gut microbiota on anti-cancer drugs: Mechanistic perspectives. *Biochim Biophys Acta Rev Cancer* 2021; **1875**: 188494 [PMID: [33346129](#) DOI: [10.1016/j.bbcan.2020.188494](#)]
- 162 **Zhou A**, Lei Y, Tang L, Hu S, Yang M, Wu L, Yang S, Tang B. Gut Microbiota: the Emerging Link to Lung Homeostasis and Disease. *J Bacteriol* 2021; **203** [PMID: [33077630](#) DOI: [10.1128/JB.00454-20](#)]
- 163 **Rawat K**, Singh N, Kumari P, Saha L. A review on preventive role of ketogenic diet (KD) in CNS disorders from the gut microbiota perspective. *Rev Neurosci* 2021; **32**: 143-157 [PMID: [33070123](#) DOI: [10.1515/revneuro-2020-0078](#)]
- 164 **Fan X**, Jin Y, Chen G, Ma X, Zhang L. Gut Microbiota Dysbiosis Drives the Development of Colorectal Cancer. *Digestion* 2021; **102**: 508-515 [PMID: [32932258](#) DOI: [10.1159/000508328](#)]
- 165 **Gasmi A**, Mujawdiya PK, Pivina L, Doşa A, Semenova Y, Benahmed AG, Bjørklund G. Relationship between Gut Microbiota, Gut Hyperpermeability and Obesity. *Curr Med Chem* 2021; **28**: 827-839 [PMID: [32693755](#) DOI: [10.2174/0929867327666200721160313](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

