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# Role of Gut Microbiota in chronic disease

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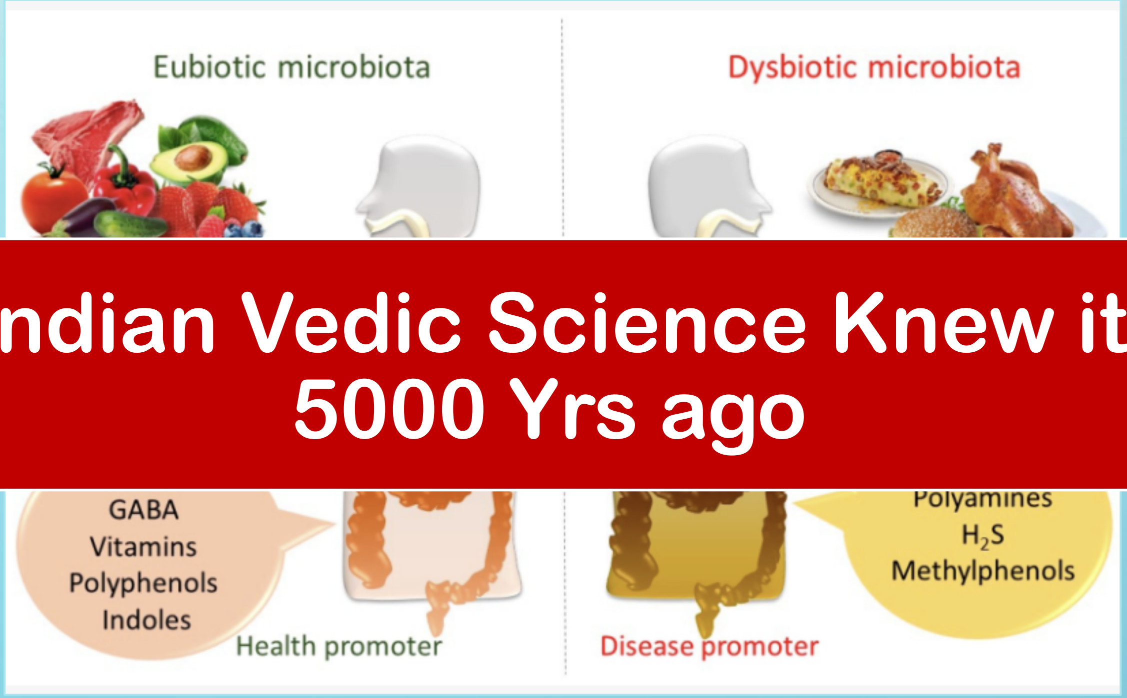
# Two thousand years ago, Hippocrates said, "All diseases begin in the gut," a statement accurately associated with immune system dysregulation and susceptibility to disease

Charak Samhita 1.39 | resanskrit.com

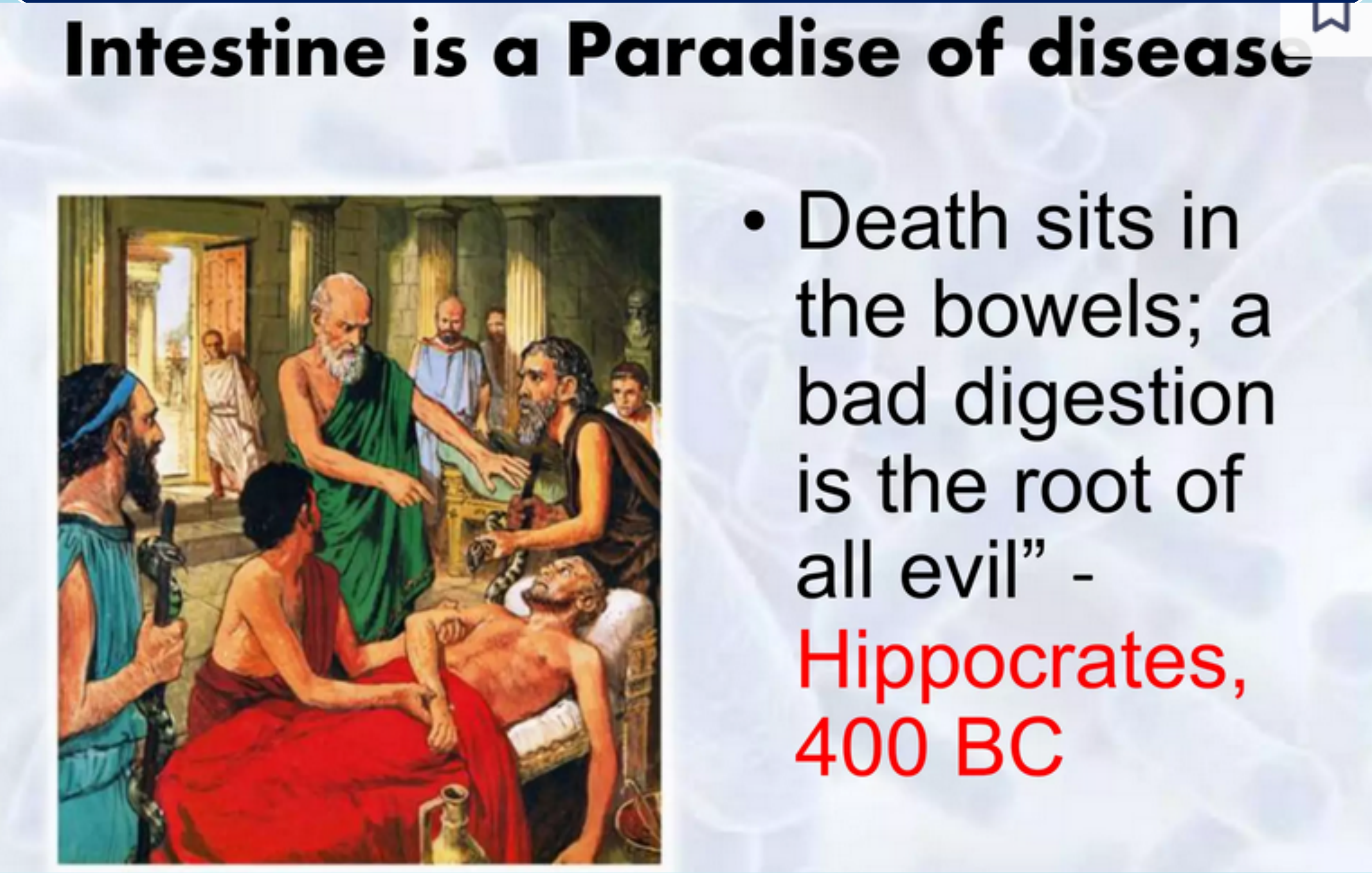
हिताहितं सुखं दुःखं आयुः तस्य हिताहितं।
मानं च तच्च यत्रोक्तं आयुर्वेदः स उच्यते॥



**Indian Vedic Science Knew it 5000 Yrs ago**

The relationships between gut microbiota and diabetes mellitus, and treatments for diabetes mellitus. Craciun CI, Neag MA, Catinean A, et al. https://doi.org/10.3390/biomedicines10020308 Biomedicines. 2022;10

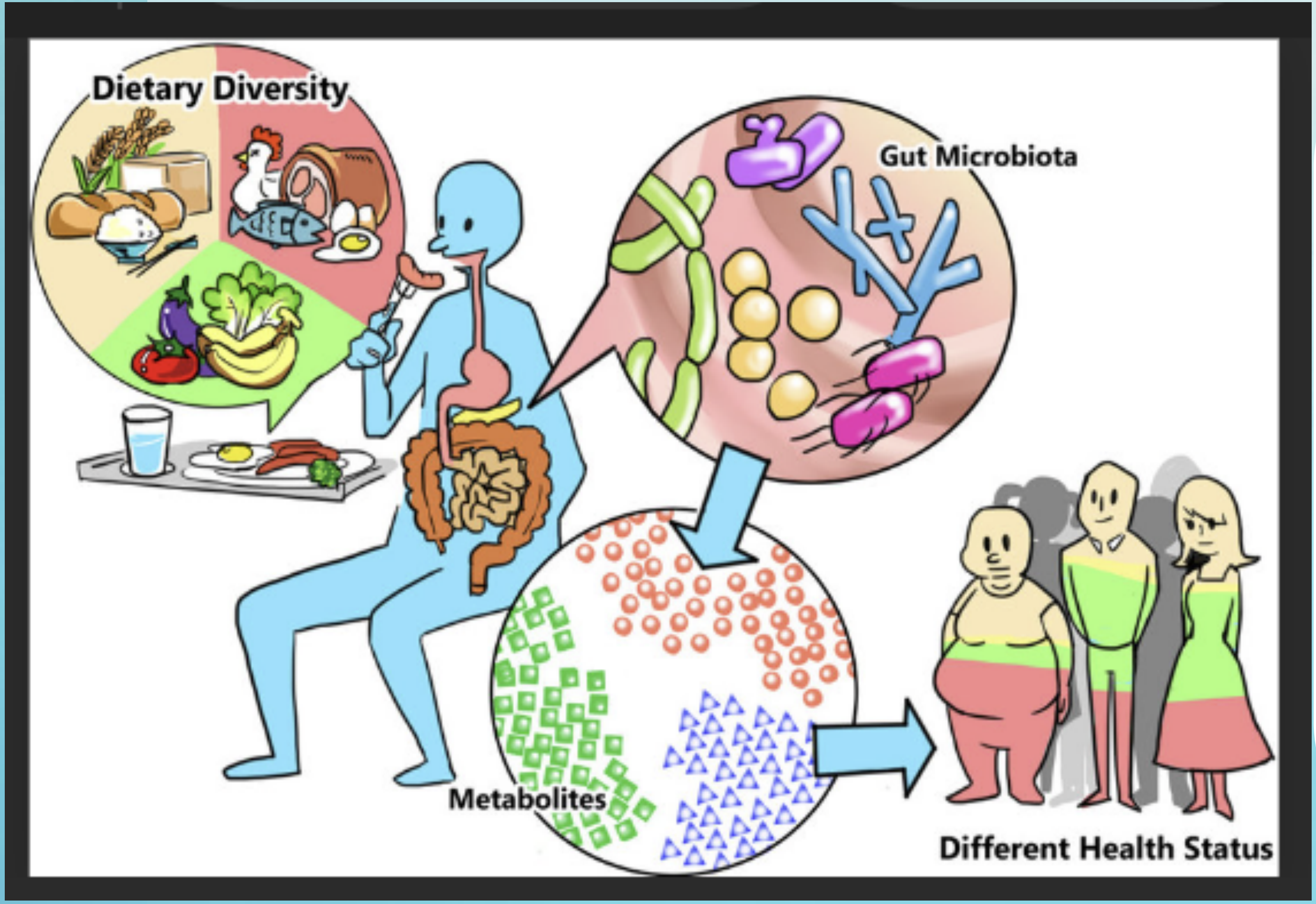
# WHY ?



## Intestine is a Paradise of disease

- Death sits in the bowels; a bad digestion is the root of all evil” - Hippocrates, 400 BC

# The gastrointestinal tract has a complex and distinct population of microorganisms that comprise the gut microbiota



The gut microbiome and its relationship with health and disease have been subject to extensive research, and the gut microbiome has been shown to be involved in maintaining human metabolism, nutrition, physiology, immune function, and mental health.

# “Human microbiome”

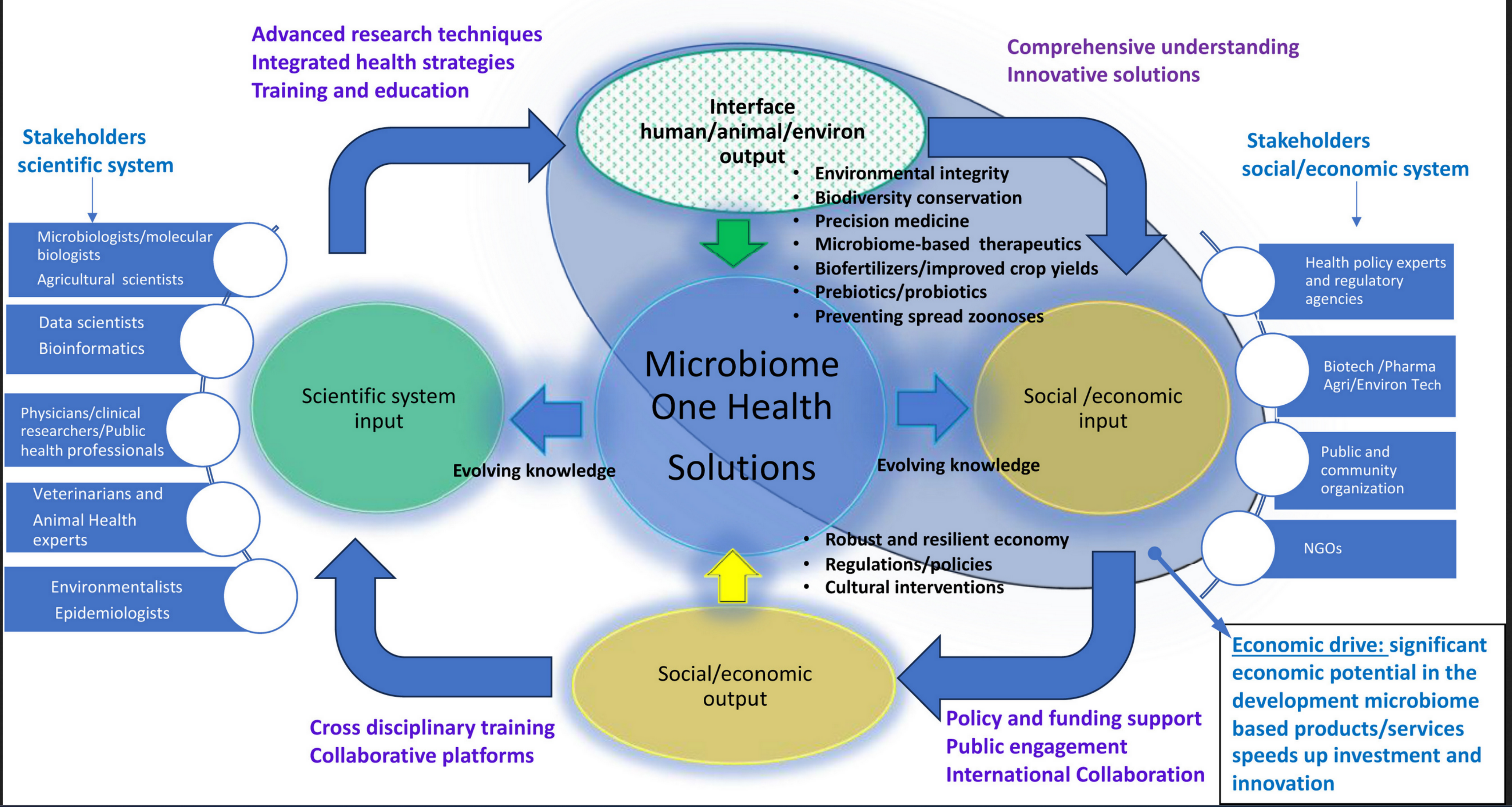
The science is exploding and we are just in the early stages of making some sense of it all

Amazing

You move with 1.5-2 kg Microbiota unknowingly in your body

People are sampling their own feces for the purposes of science taking probiotics, eating loads of yogurt, kombucha or kimchi – and try to foster the “good” bacteria.

# Scenario 10 Years Later



Advanced research techniques
Integrated health strategies
Training and education

Comprehensive understanding
Innovative solutions

Stakeholders
scientific system

- Microbiologists/molecular biologists
  Agricultural scientists
- Data scientists
  Bioinformatics
- Physicians/clinical researchers/Public health professionals
- Veterinarians and Animal Health experts
- Environmentalists
  Epidemiologists

Interface
human/animal/environ
output

- Environmental integrity
- Biodiversity conservation
- Precision medicine
- Microbiome-based therapeutics
- Biofertilizers/improved crop yields
- Prebiotics/probiotics
- Preventing spread zoonoses

Scientific system input

Evolving knowledge

Microbiome
One Health
Solutions

Evolving knowledge

Social /economic input

Stakeholders
social/economic system

- Health policy experts and regulatory agencies
- Biotech /Pharma
  Agri/Environ Tech
- Public and community organization
- NGOs

- Robust and resilient economy
- Regulations/policies
- Cultural interventions

Social/economic output

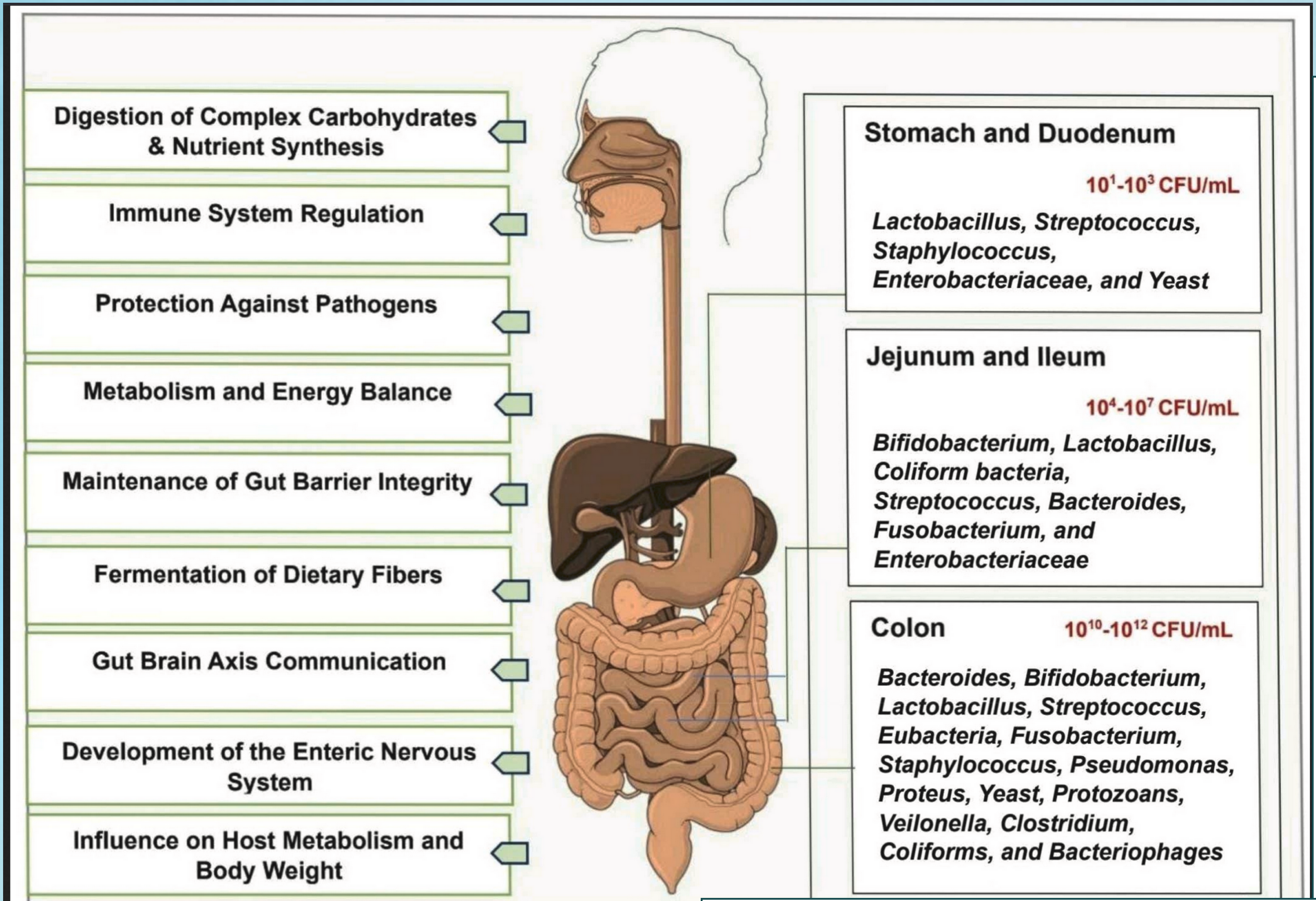
Cross disciplinary training
Collaborative platforms

Policy and funding support
Public engagement
International Collaboration

<u>Economic drive:</u> significant economic potential in the development microbiome based products/services speeds up investment and innovation

# Lets see what in 2025?

The human gut microbiome is a bustling metropolis of microbial life, thriving with a staggering number of microbial residents that form a complex and dynamic ecosystem within mammalian bodies.



Digestion of Complex Carbohydrates & Nutrient Synthesis

Immune System Regulation

Protection Against Pathogens

Metabolism and Energy Balance

Maintenance of Gut Barrier Integrity

Fermentation of Dietary Fibers

Gut Brain Axis Communication

Development of the Enteric Nervous System

Influence on Host Metabolism and Body Weight

**Stomach and Duodenum**

$10^1$-$10^3$ CFU/mL

*Lactobacillus, Streptococcus, Staphylococcus, Enterobacteriaceae, and Yeast*

**Jejunum and Ileum**

$10^4$-$10^7$ CFU/mL

*Bifidobacterium, Lactobacillus, Coliform bacteria, Streptococcus, Bacteroides, Fusobacterium, and Enterobacteriaceae*

**Colon** $10^{10}$-$10^{12}$ CFU/mL

*Bacteroides, Bifidobacterium, Lactobacillus, Streptococcus, Eubacteria, Fusobacterium, Staphylococcus, Pseudomonas, Proteus, Yeast, Protozoans, Veilonella, Clostridium, Coliforms, and Bacteriophages*

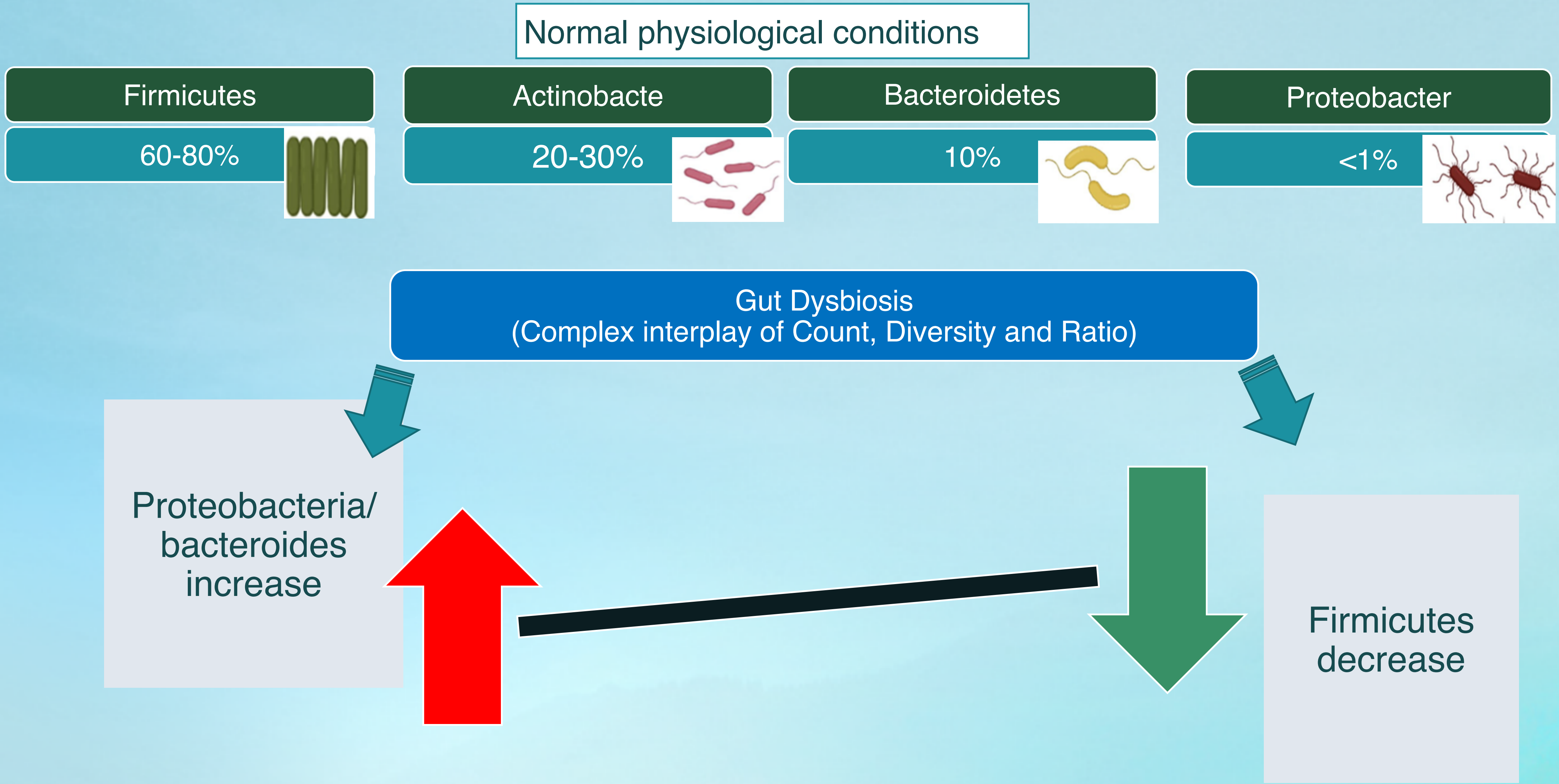
1. Each region is habitat to a distinct microbial community that is crucial for various physiological functions.

2. The gastrointestinal tract exhibits great variation in the quantities of these organisms, which are expressed in colony-forming units per millilitre (CFU/mL).

3. This variation is indicative of the distinct biological niches and metabolic processes that exist within each

https://doi.org/10.1016/j.medmic.2024.100106

# Gut Microbiota 4 Major Phyla



Normal physiological conditions

| Firmicutes | Actinobacte | Bacteroidetes | Proteobacter |
|---|---|---|---|
| 60-80% | 20-30% | 10% | <1% |

Gut Dysbiosis
(Complex interplay of Count, Diversity and Ratio)

Proteobacteria/ bacteroides increase

Firmicutes decrease

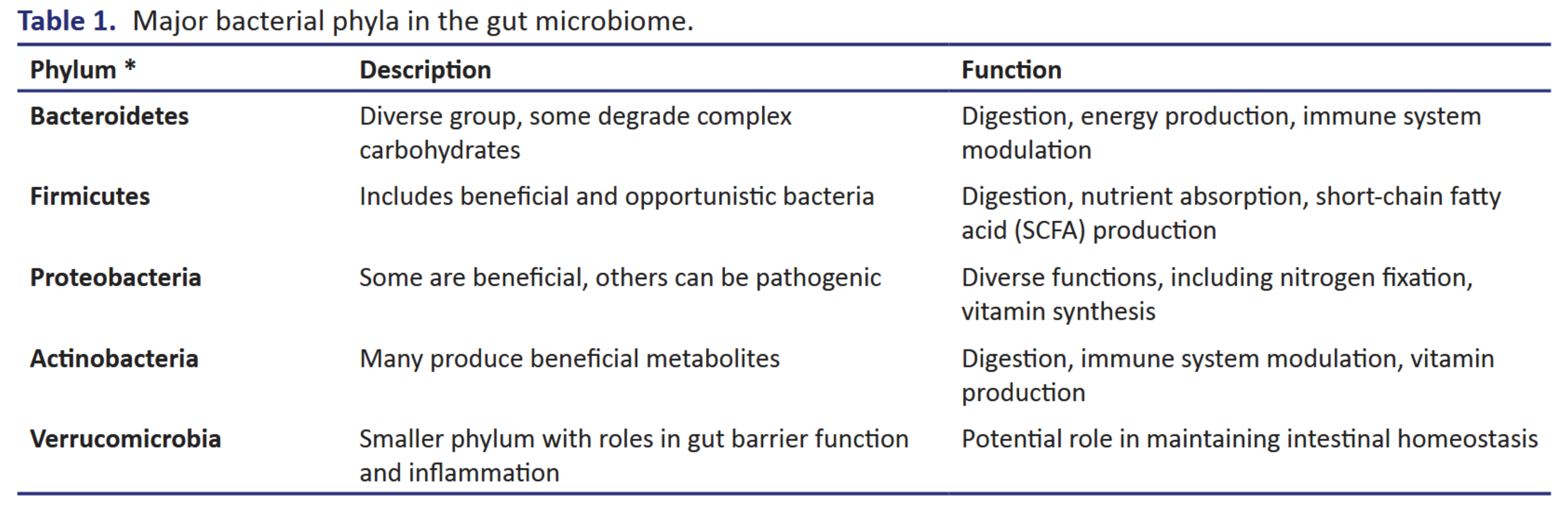
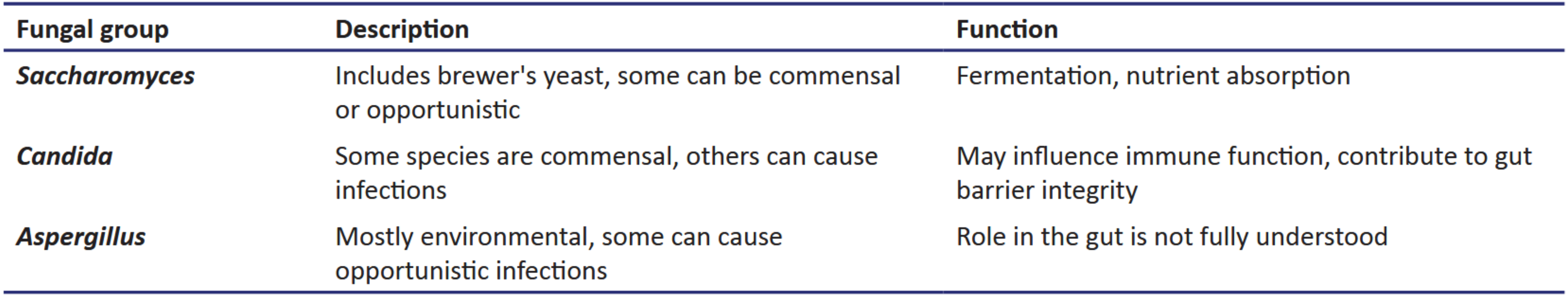


**Table 1.** Major bacterial phyla in the gut microbiome.

| Phylum * | Description | Function |
|---|---|---|
| **Bacteroidetes** | Diverse group, some degrade complex carbohydrates | Digestion, energy production, immune system modulation |
| **Firmicutes** | Includes beneficial and opportunistic bacteria | Digestion, nutrient absorption, short-chain fatty acid (SCFA) production |
| **Proteobacteria** | Some are beneficial, others can be pathogenic | Diverse functions, including nitrogen fixation, vitamin synthesis |
| **Actinobacteria** | Many produce beneficial metabolites | Digestion, immune system modulation, vitamin production |
| **Verrucomicrobia** | Smaller phylum with roles in gut barrier function and inflammation | Potential role in maintaining intestinal homeostasis |

**Table 2.** Fungal composition in the gut from Ascomycota phylum.



| Fungal group | Description | Function |
|---|---|---|
| ***Saccharomyces*** | Includes brewer's yeast, some can be commensal or opportunistic | Fermentation, nutrient absorption |
| ***Candida*** | Some species are commensal, others can cause infections | May influence immune function, contribute to gut barrier integrity |
| ***Aspergillus*** | Mostly environmental, some can cause opportunistic infections | Role in the gut is not fully understood |

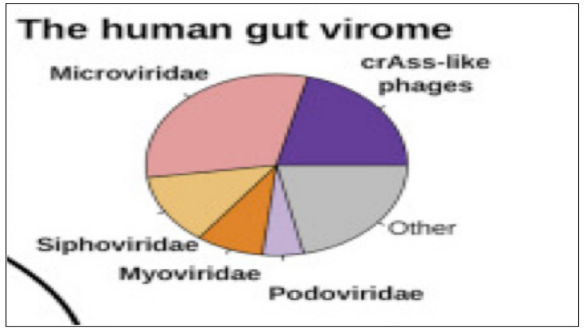
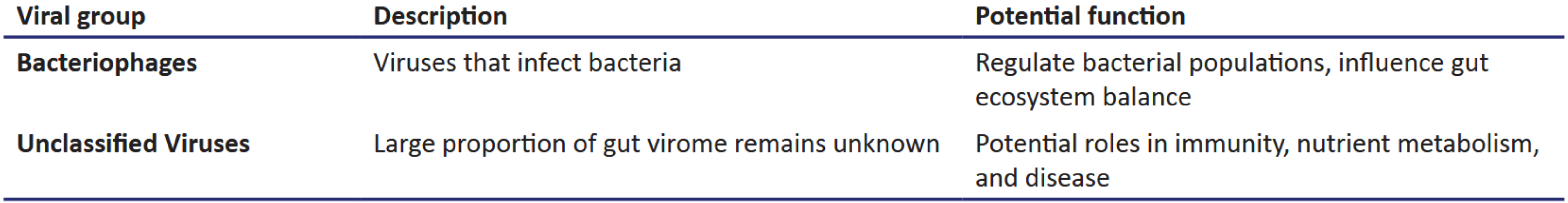


**Table 3.** Gut virome composition (limited understanding).



| Viral group | Description | Potential function |
|---|---|---|
| **Bacteriophages** | Viruses that infect bacteria | Regulate bacterial populations, influence gut ecosystem balance |
| **Unclassified Viruses** | Large proportion of gut virome remains unknown | Potential roles in immunity, nutrient metabolism, and disease |

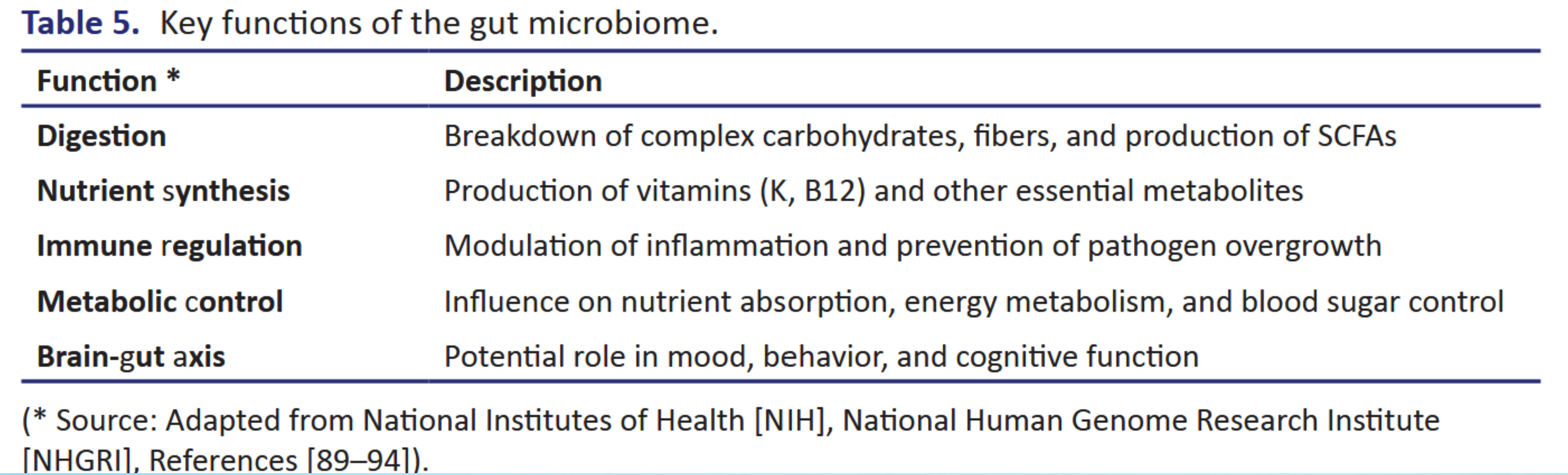


**Table 5.** Key functions of the gut microbiome.

| Function * | Description |
|---|---|
| **Digestion** | Breakdown of complex carbohydrates, fibers, and production of SCFAs |
| **Nutrient synthesis** | Production of vitamins (K, B12) and other essential metabolites |
| **Immune regulation** | Modulation of inflammation and prevention of pathogen overgrowth |
| **Metabolic control** | Influence on nutrient absorption, energy metabolism, and blood sugar control |
| **Brain-gut axis** | Potential role in mood, behavior, and cognitive function |

(* Source: Adapted from National Institutes of Health [NIH], National Human Genome Research Institute [NHGRI], References [89–94]).

The gut microbiome and its impact on human health. (Source: https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-017-1175-y, https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-022-03296-9 and https://www.nature.com/articles/s41392-022-00974-4)

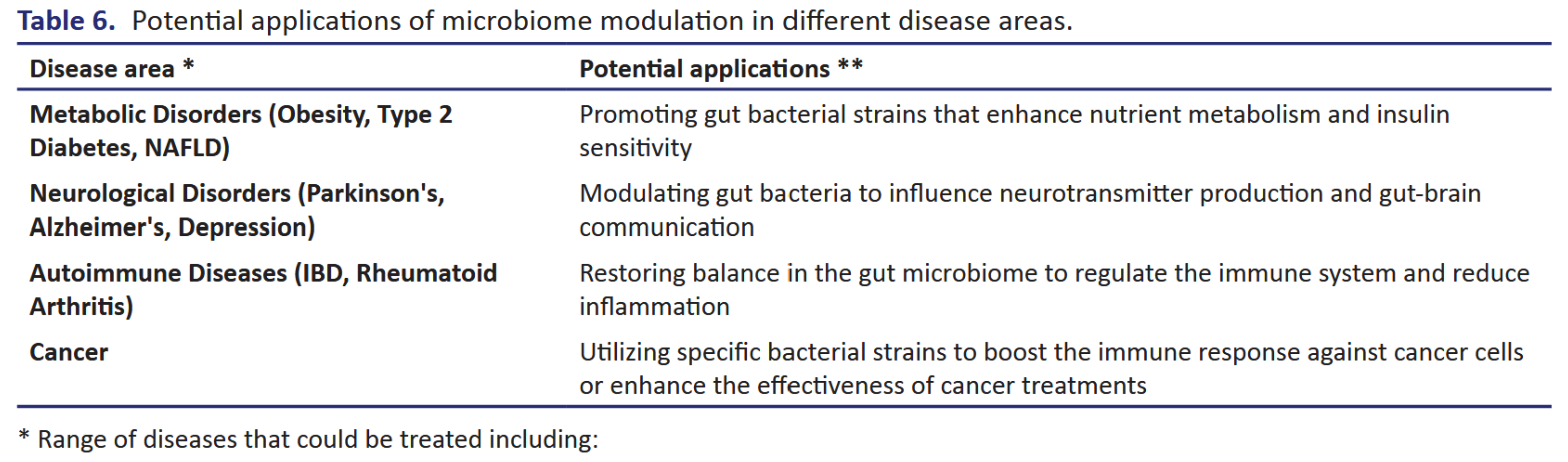
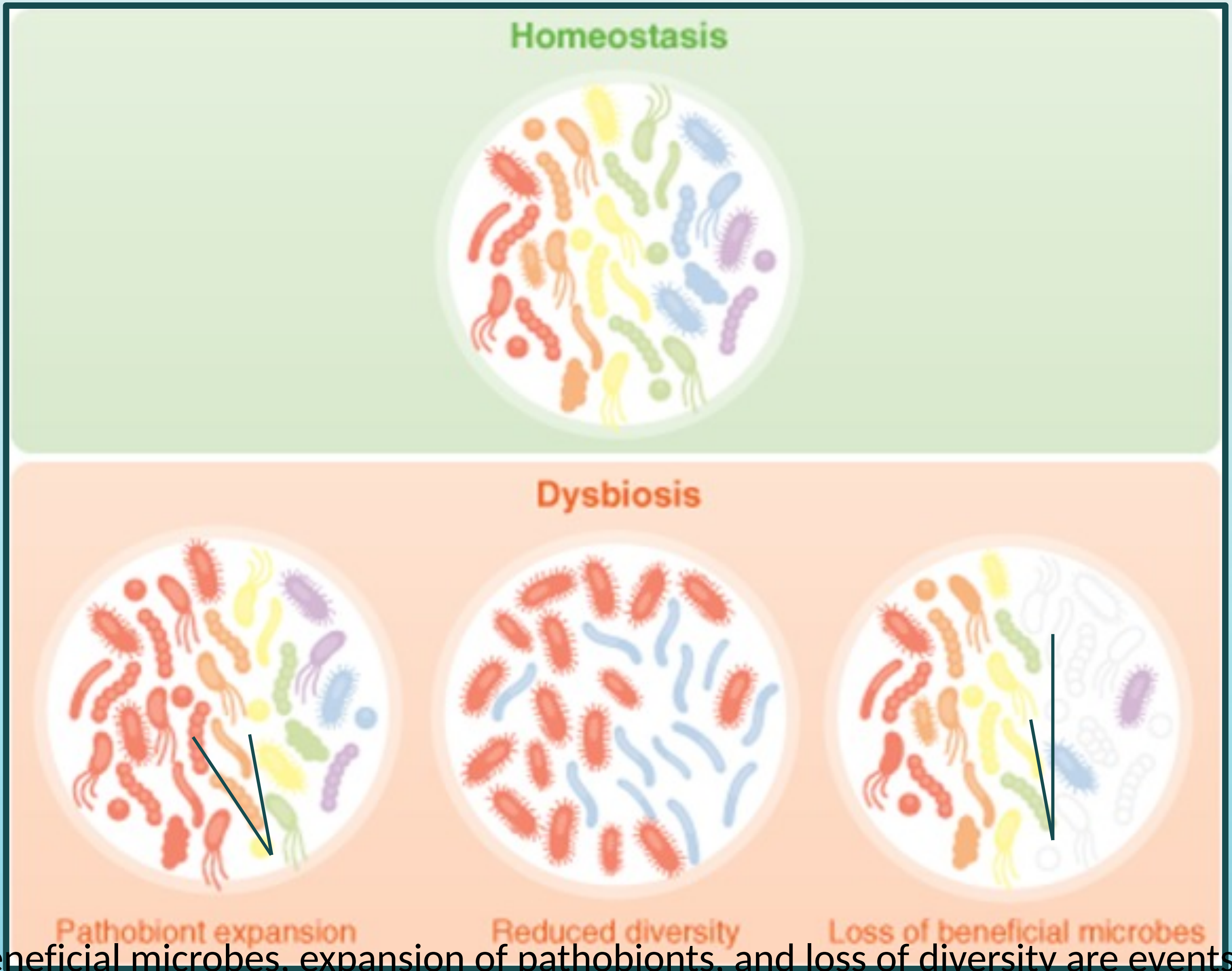


**Table 6.** Potential applications of microbiome modulation in different disease areas.

| Disease area * | Potential applications ** |
|---|---|
| **Metabolic Disorders (Obesity, Type 2 Diabetes, NAFLD)** | Promoting gut bacterial strains that enhance nutrient metabolism and insulin sensitivity |
| **Neurological Disorders (Parkinson's, Alzheimer's, Depression)** | Modulating gut bacteria to influence neurotransmitter production and gut-brain communication |
| **Autoimmune Diseases (IBD, Rheumatoid Arthritis)** | Restoring balance in the gut microbiome to regulate the immune system and reduce inflammation |
| **Cancer** | Utilizing specific bacterial strains to boost the immune response against cancer cells or enhance the effectiveness of cancer treatments |

* Range of diseases that could be treated including:

# Gut microbiota and how they differ in intestinal homoeostasis vs dysbiosis.



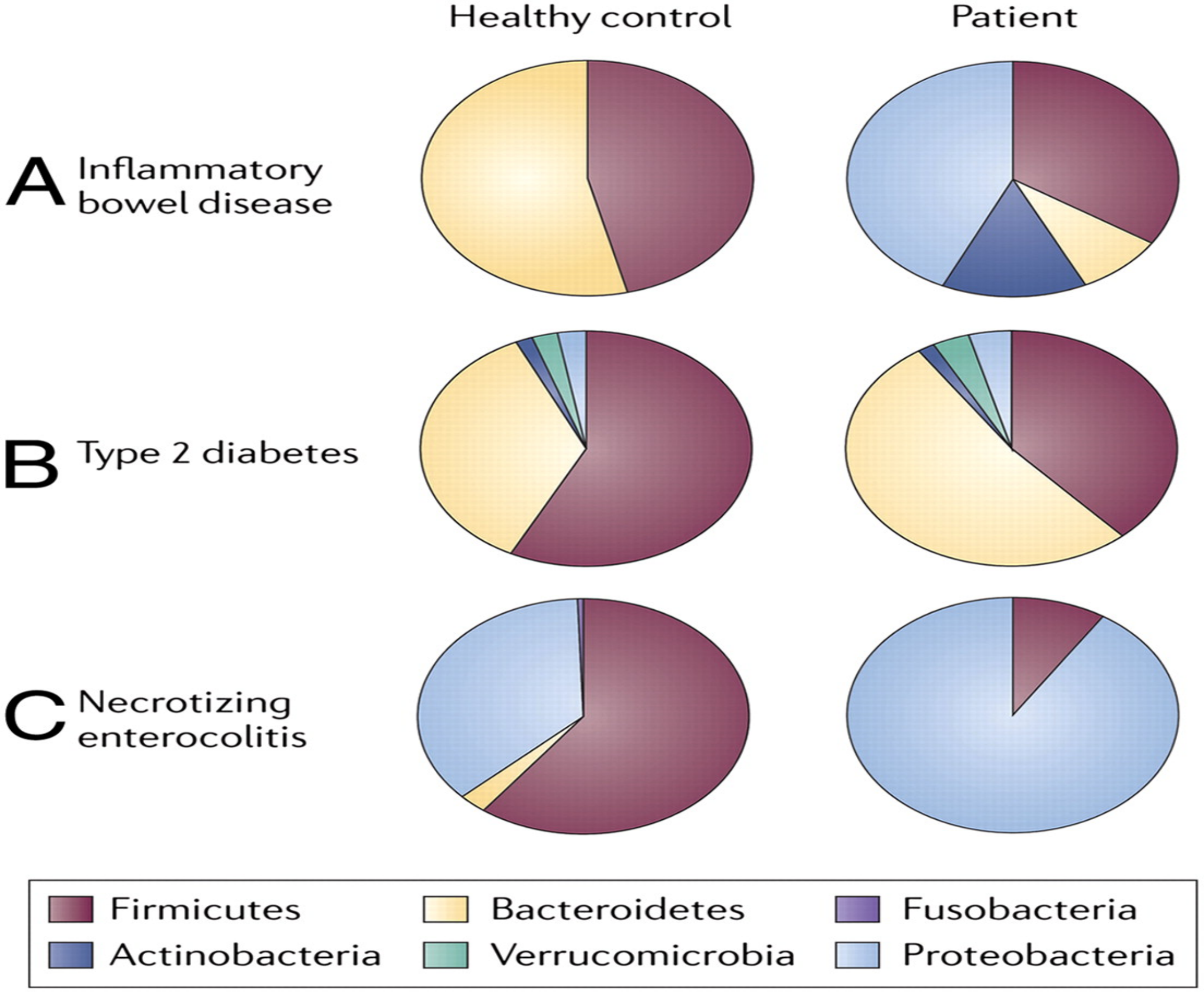
A loss of beneficial microbes, expansion of pathobionts, and loss of diversity are events that encompass dysbiosis.

Cell Microbiol. 2014 Jul;16(7):1024-33

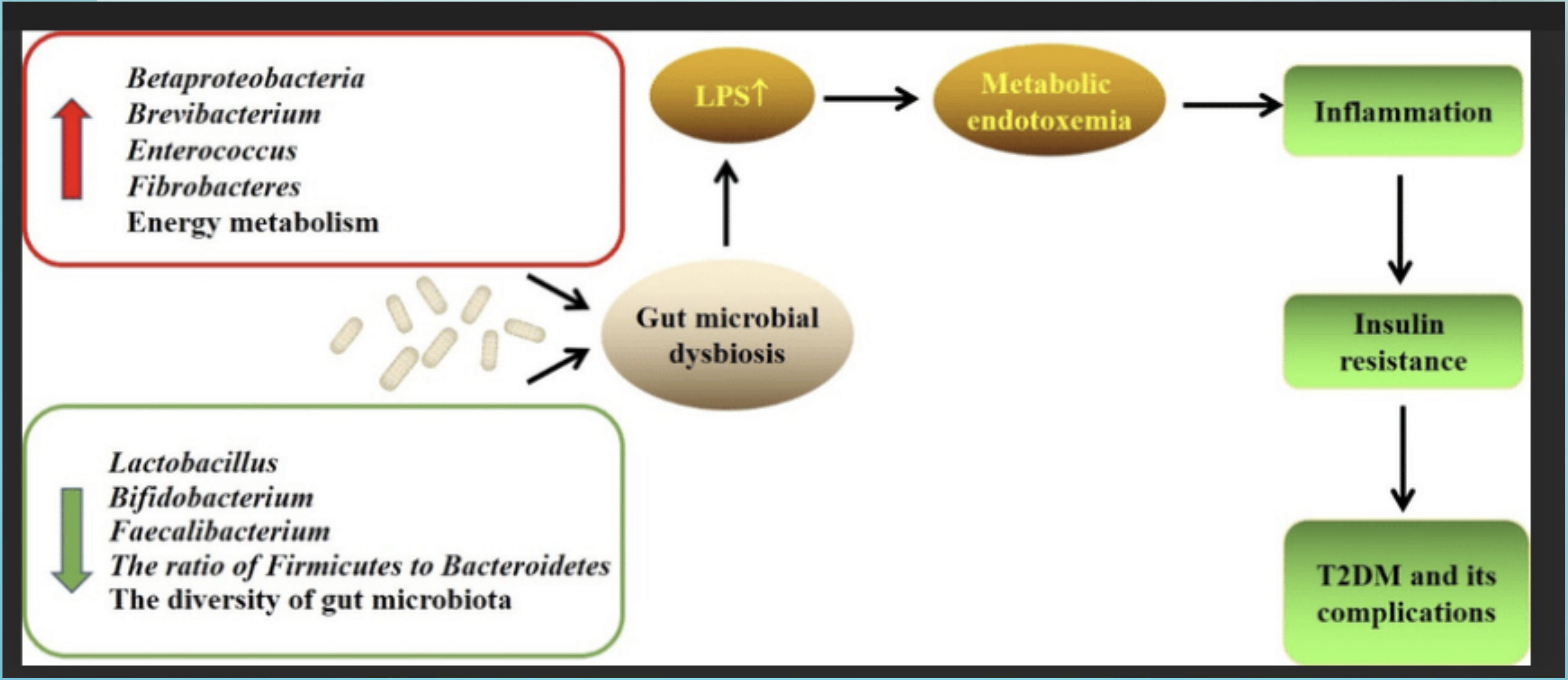
# Gut Dysbiosis
# (Complex interplay of Count, Diversity and Ratio)

Proteobacteria/ bacteroides increase

Firmicutes decrease



# As many treatment options target the microbiota, a bidirectional relationship between diabetes and the gut microbiota can be observed.



# Gut Micobial Dysbiosis

1. Affects the production of SCFA (Short chain fatty acid)
2. Enhanced intestinal LPS ( Lipopolysaccharide) permeability
3. Altered bile acid profile and the endocannabinoid system

**Insulin Sensitivity ↓**

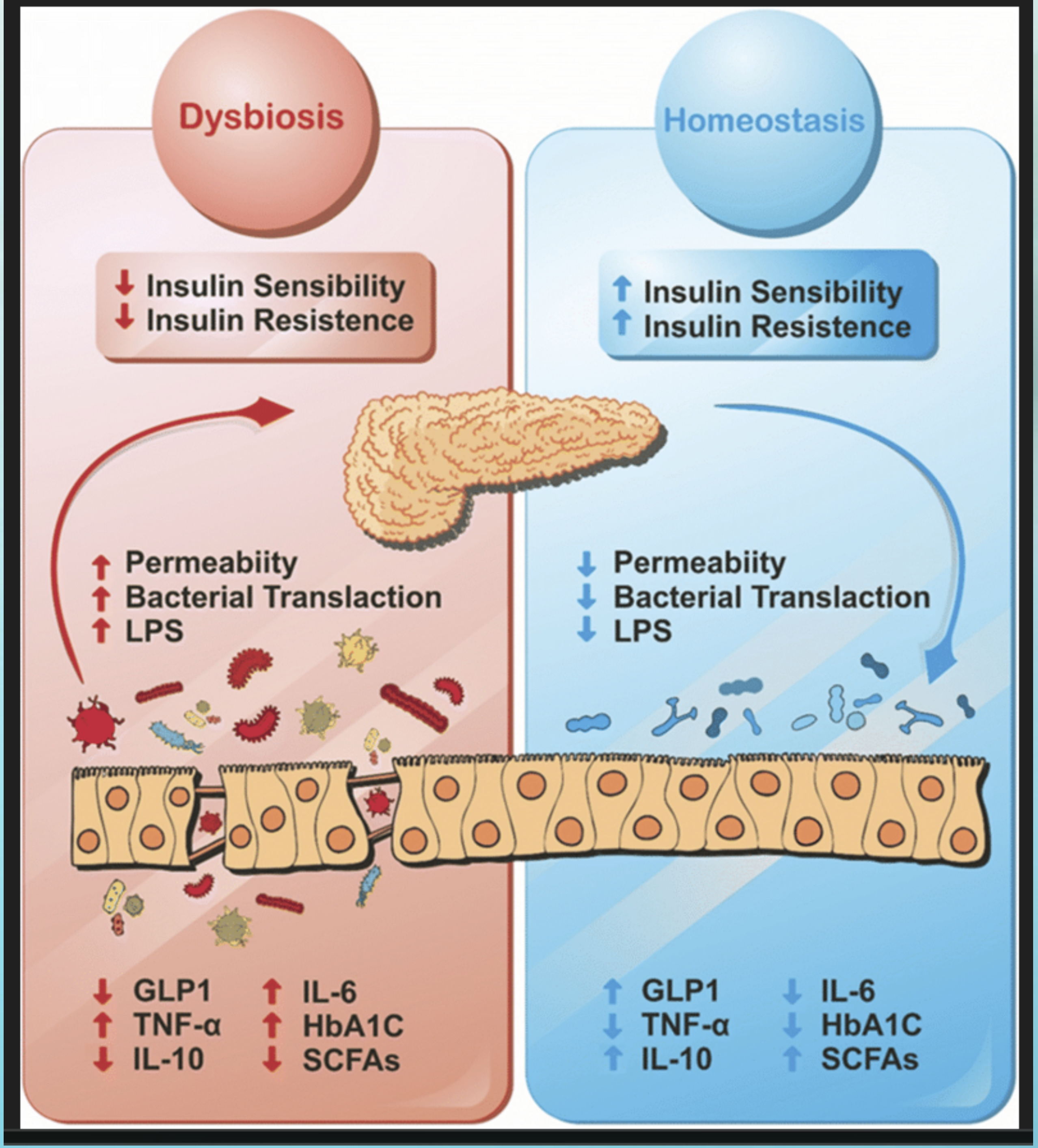
**Induces Insulin Resistance**

↑
- Permeability
- Bacterial Translaction
- LPS

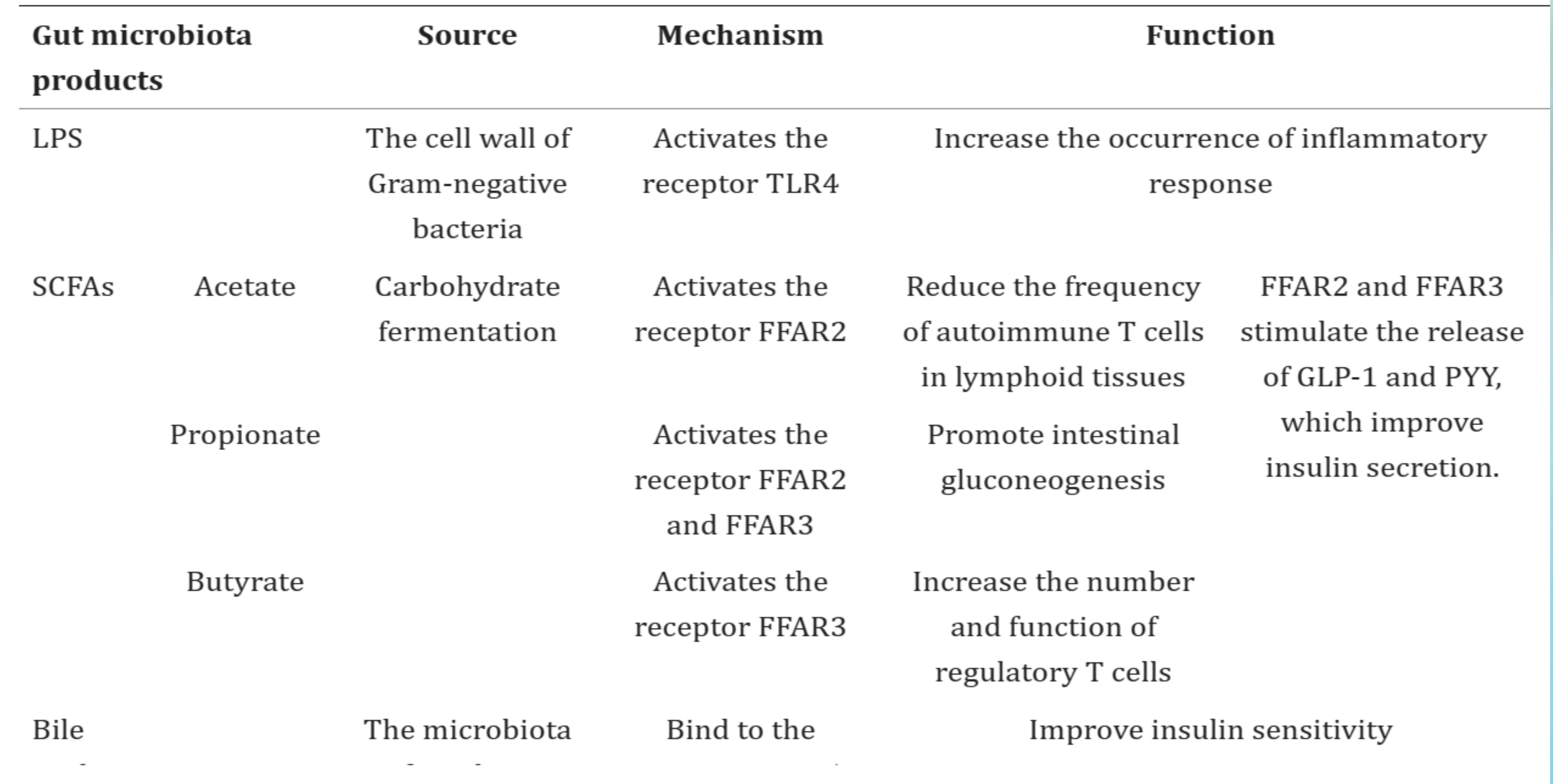
**Metabolic Endotoxemia**

# Connecting Chronic Diseases

# Now Showing actors in Film called Gut Microbiota



# Products of gut microbiota and their mechanism of action



| Gut microbiota products | | Source | Mechanism | Function | |
|---|---|---|---|---|---|
| LPS | | The cell wall of Gram-negative bacteria | Activates the receptor TLR4 | Increase the occurrence of inflammatory response | |
| SCFAs | Acetate | Carbohydrate fermentation | Activates the receptor FFAR2 | Reduce the frequency of autoimmune T cells in lymphoid tissues | FFAR2 and FFAR3 stimulate the release of GLP-1 and PYY, which improve insulin secretion. |
| | Propionate | | Activates the receptor FFAR2 and FFAR3 | Promote intestinal gluconeogenesis | |
| | Butyrate | | Activates the receptor FFAR3 | Increase the number and function of regulatory T cells | |
| Bile | | The microbiota | Bind to the | Improve insulin sensitivity | |

LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; SCFAs: Short-chain fatty acids; FFAR 2: Free fatty acid receptor 2; FFAR 3: Free fatty acid receptor 3; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY; TGR5: Takeda G protein-coupled receptor 5; FXR: Farnesoid X receptor; BCAA: Branched-Chain Amino Acids; PI3K: Phosphatidylinositol 3-kinase.

# Microbiota influence on glucose homeostasis

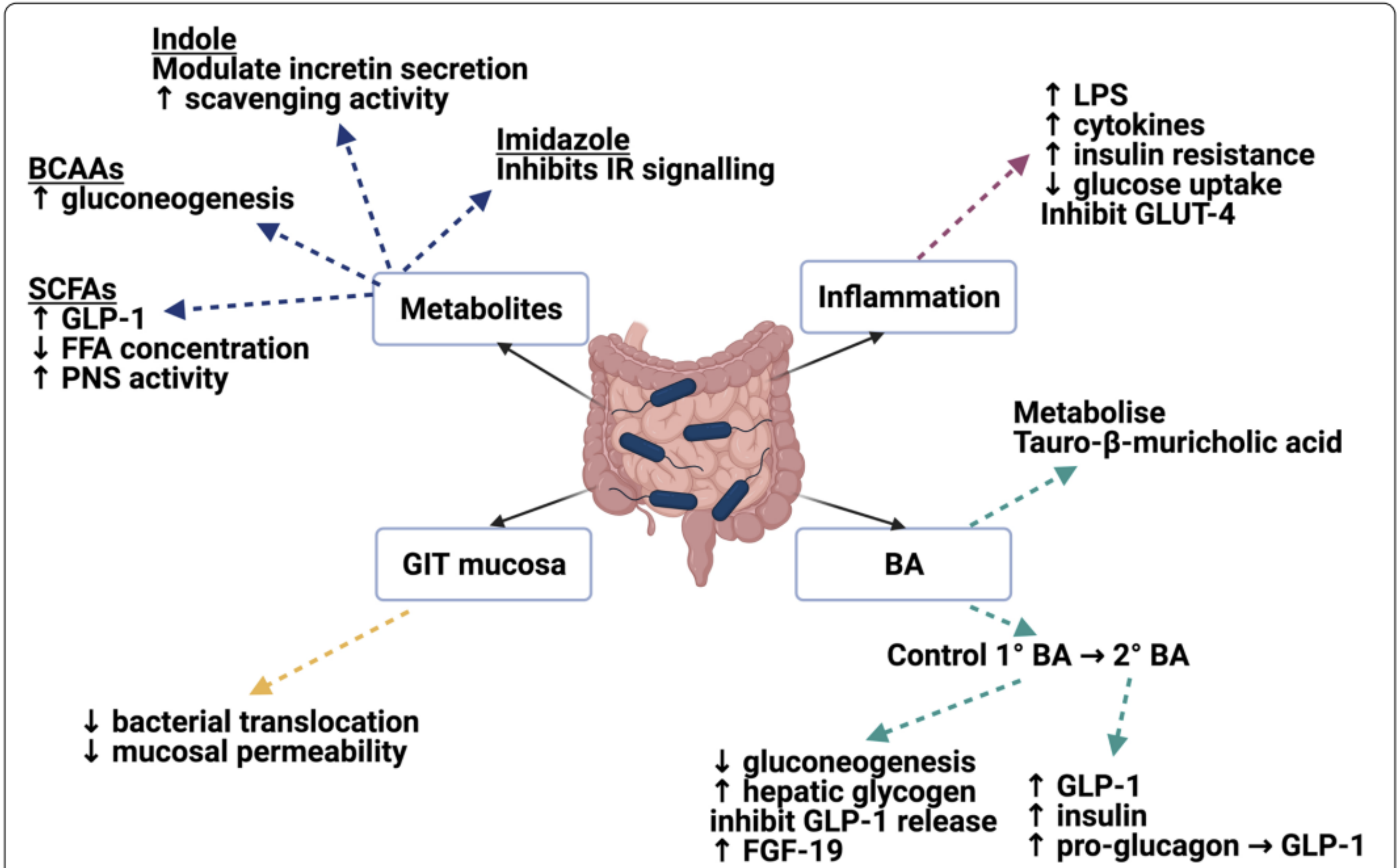
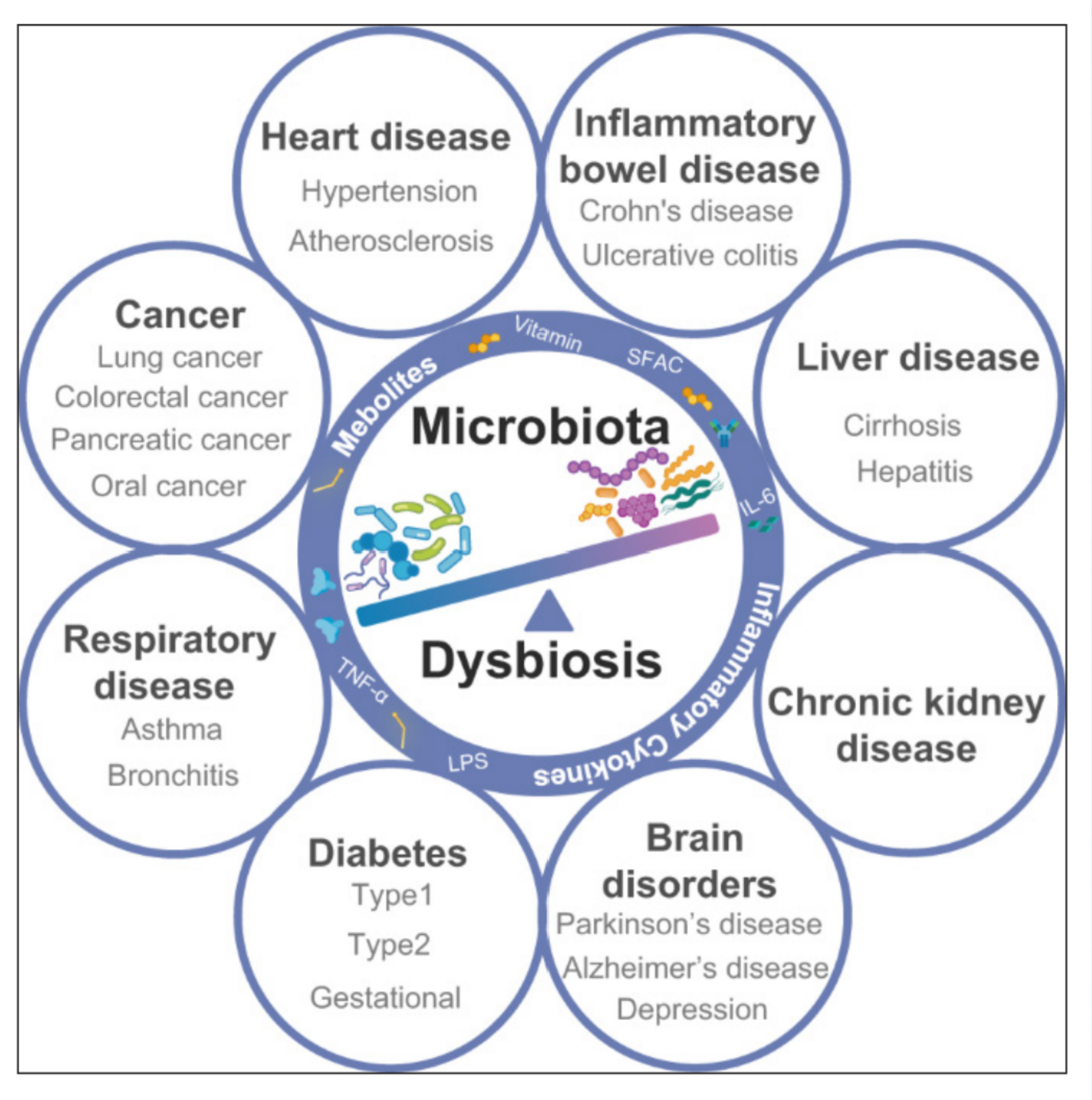


**Fig. 1** Microbiota influence on glucose homeostasis

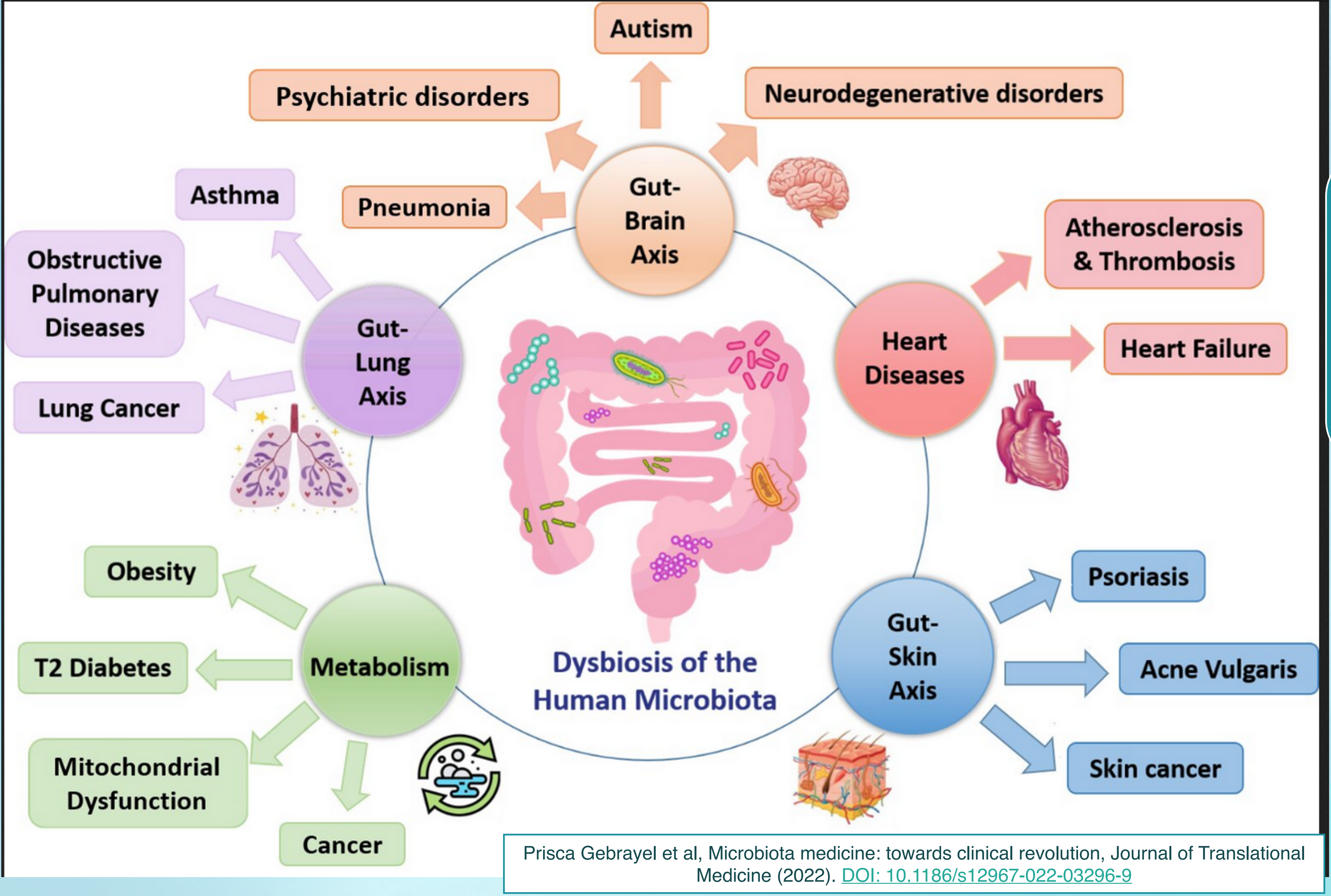
Cunningham, A.L., Stephens, J.W. & Harris, D.A. Gut microbiota influence in type 2 diabetes mellitus (T2DM). *Gut Pathog* **13**, 50 (2021). https://doi.org/10.1186/s13099-021-00446-0

# The gut-kidney axis



Microbiome modulation strategies in translational medicine (Source: https://www.nature.com/articles/s41388-020-1341-1, https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-022-03378-8 and https://www.mdpi.com/2079-6382/11/4/474)

# Microbiota medicine: Towards clinical revolution

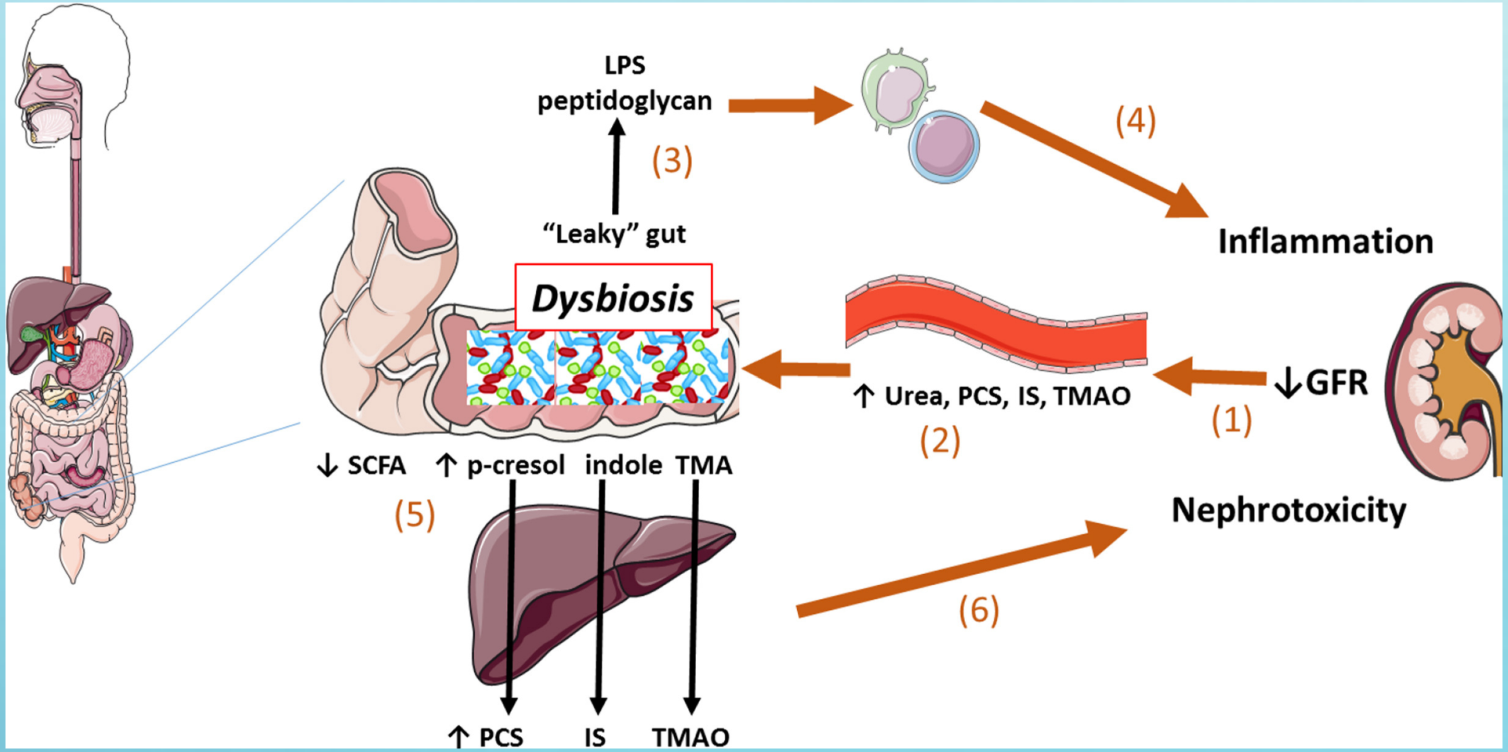


Prisca Gebrayel et al, Microbiota medicine: towards clinical revolution, Journal of Translational Medicine (2022). DOI: 10.1186/s12967-022-03296-9

# Mounting evidence supports a bidirectional microbiota-kidney crosstalk, which becomes particularly manifest during progressive kidney dysfunction.

- In chronic kidney disease (CKD), the “healthy” microbiota structure is disrupted and intestinal microbes produce large quantities of uremic solutes responsible for renal damage;

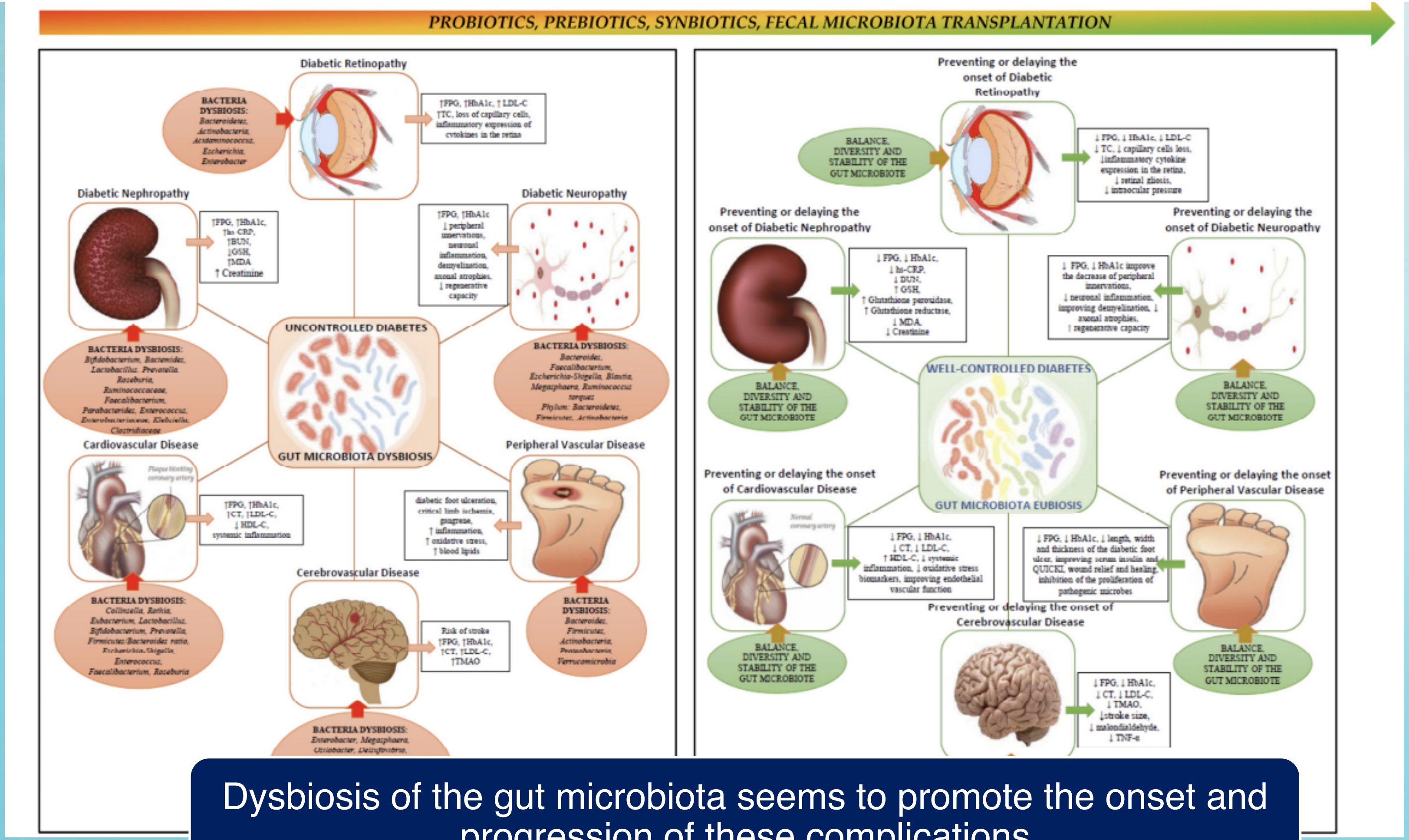
- On the other hand, the uremic state, fueled by reduced renal clearance, causes shifts in microbial metabolism and composition, hence creating a vicious cycle in which dysbiosis and renal dysfunction are progressively worsene



C.M. Mosterd, M. Kanbay, B.J.H. van den Born, D.H. van Raalte, E. Rampanelli,
Intestinal microbiota and diabetic kidney diseases: the Role of microbiota and derived metabolites inmodulation of renal inflammation and disease progression,Best Practice & Research Clinical Endocrinology & Metabolism, Volume 35, Issue 3,2021,https://doi.org/10.1016/

j.beem.2021.101484.

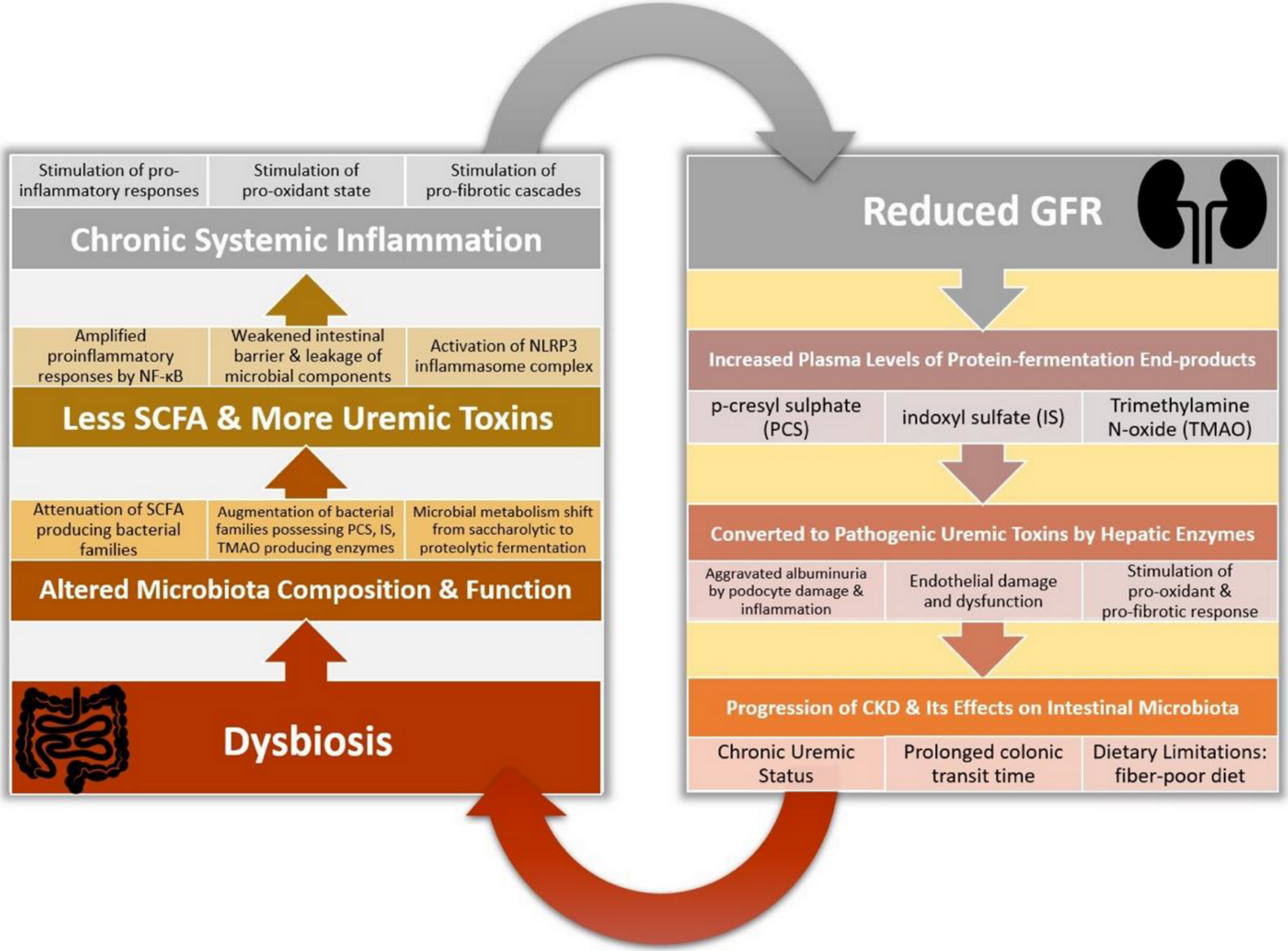
# Chronic micro- and macrovascular complications of diabetes, and associated changes in the composition of the gut microbiota. Poorly controlled diabetes leads to chronic complications over time



Dysbiosis of the gut microbiota seems to promote the onset and progression of these complications

The right panel depicts the potential effects of restoring gut microbiota eubiosis in ameliorating, preventing or delaying the onset of chronic complications of diabetes, via probiotics, prebiotics, symbiotics or by fecal microbiota transplantation. ↑, increase; ↓,

Iatcu, C.O.; Steen, A.; Covasa, M. Gut Microbiota and Complications of Type-2 Diabetes. Nutrients 2022, 14, 166. https:// doi.org/10.3390/nu14010166



Stimulation of pro-inflammatory responses

Stimulation of pro-oxidant state

Stimulation of pro-fibrotic cascades

**Chronic Systemic Inflammation**

Amplified proinflammatory responses by NF-κB

Weakened intestinal barrier & leakage of microbial components

Activation of NLRP3 inflammasome complex

**Less SCFA & More Uremic Toxins**

Attenuation of SCFA producing bacterial families

Augmentation of bacterial families possessing PCS, IS, TMAO producing enzymes

Microbial metabolism shift from saccharolytic to proteolytic fermentation

**Altered Microbiota Composition & Function**

**Dysbiosis**

**Reduced GFR**

**Increased Plasma Levels of Protein-fermentation End-products**

p-cresyl sulphate (PCS)

indoxyl sulfate (IS)

Trimethylamine N-oxide (TMAO)

**Converted to Pathogenic Uremic Toxins by Hepatic Enzymes**

Aggravated albuminuria by podocyte damage & inflammation

Endothelial damage and dysfunction

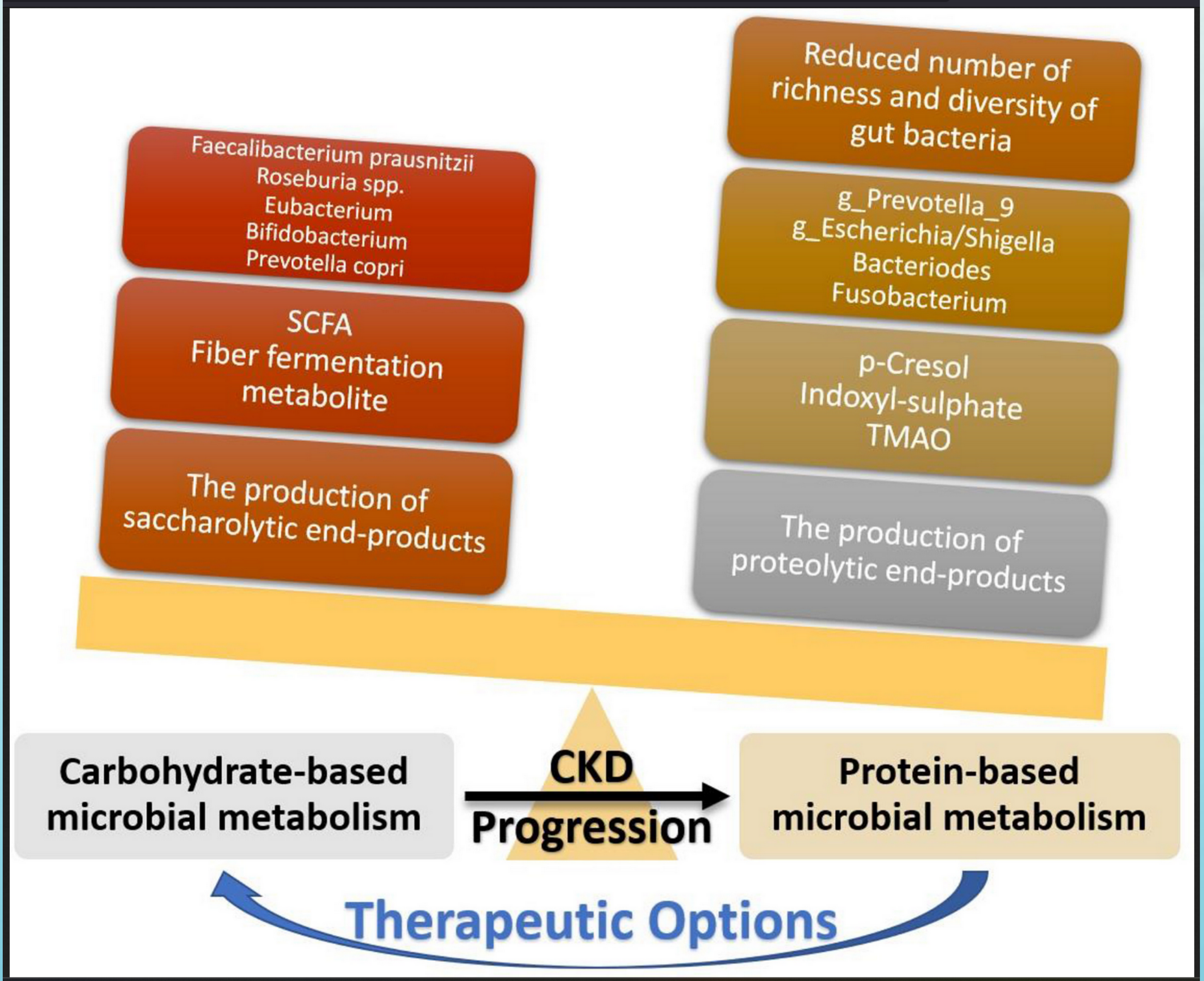
Stimulation of pro-oxidant & pro-fibrotic response

**Progression of CKD & Its Effects on Intestinal Microbiota**

Chronic Uremic Status

Prolonged colonic transit time

Dietary Limitations: fiber-poor diet



Faecalibacterium prausnitzii
Roseburia spp.
Eubacterium
Bifidobacterium
Prevotella copri

SCFA
Fiber fermentation metabolite

The production of saccharolytic end-products

Reduced number of richness and diversity of gut bacteria

g_Prevotella_9
g_Escherichia/Shigella
Bacteriodes
Fusobacterium

p-Cresol
Indoxyl-sulphate
TMAO

The production of proteolytic end-products

**Carbohydrate-based microbial metabolism**

**CKD Progression**

**Protein-based microbial metabolism**

**Therapeutic Options**

# Intestinal microbiota and diabetic kidney diseases

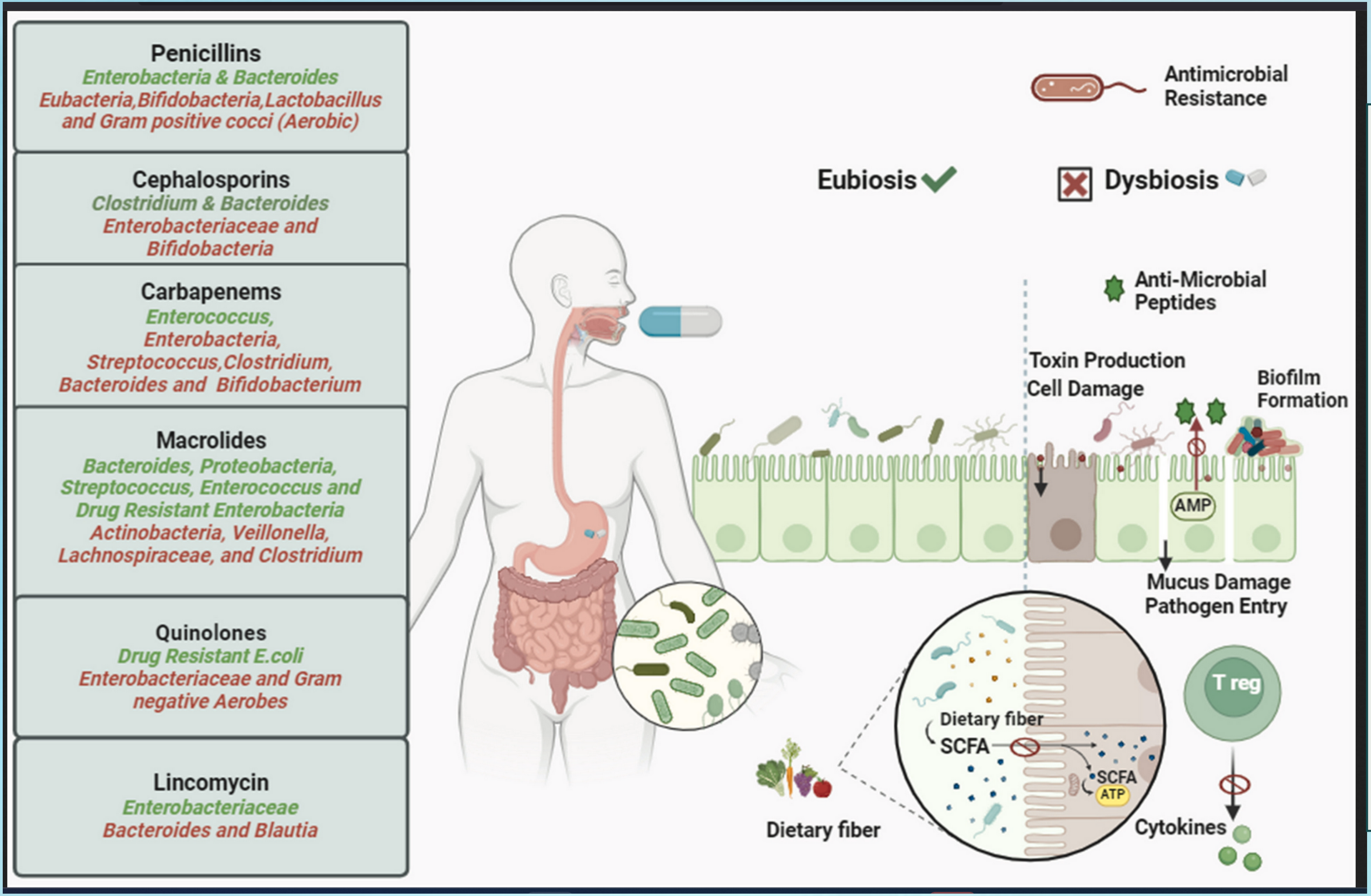
## Practice points:

- Changes in microbiota composition and function should be considered as risk factors and therapeutical targets in the management of CKD/DKD.

- Circulating levels of gut-derived uremic toxins should be measured to help assessing the risk of CV and renal complications in diabetic patients.

- DKD is largely driven by inflammatory reactions; scientific evidence shows that targeting TLRs and inflammasomes represents promising strategies to improve clinical and pathological parameters in DKD.

# Action of Antibiotics on gut cells and Microbiome



Increased Antibiotic Resistance, Toxin production, cell damage, biofilm formation, Mucus damage & pathogen entry, downregulation of cytokine production in T regulatory cells ($T_{reg}$), Antimicrobial peptides from AMP genes and ATP production from short chain Fatty Acid (SCFA) have been found down regulated as a result of antibiotic induced gut dysbiosis

Medicine in Microecology
Volume 20, June 2024, 100106

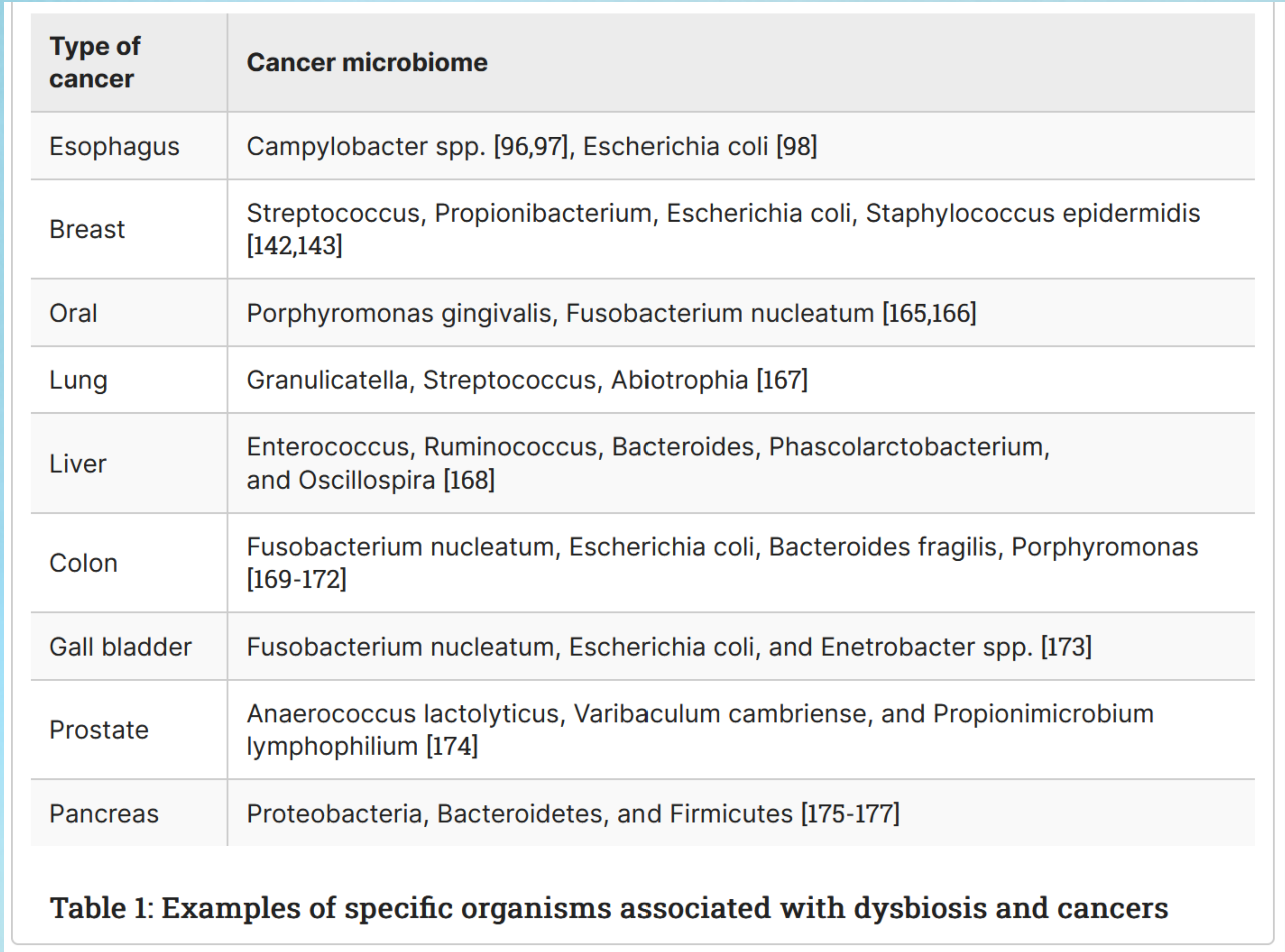
- The fine balance of the gut microbiota becomes disrupted by antibiotics, particularly broad-spectrum ones. This causes antibiotic-induced gut dysbiosis, which has far-reaching effects from infancy to adulthood.

- Antibiotic-resistant strains and resulting reduction in microbial diversity raise a number of health concerns, such as obesity, allergies, asthma, and changes in metabolism.

- There is complex connections between antibiotic resistance and cirrhosis, colorectal cancer,

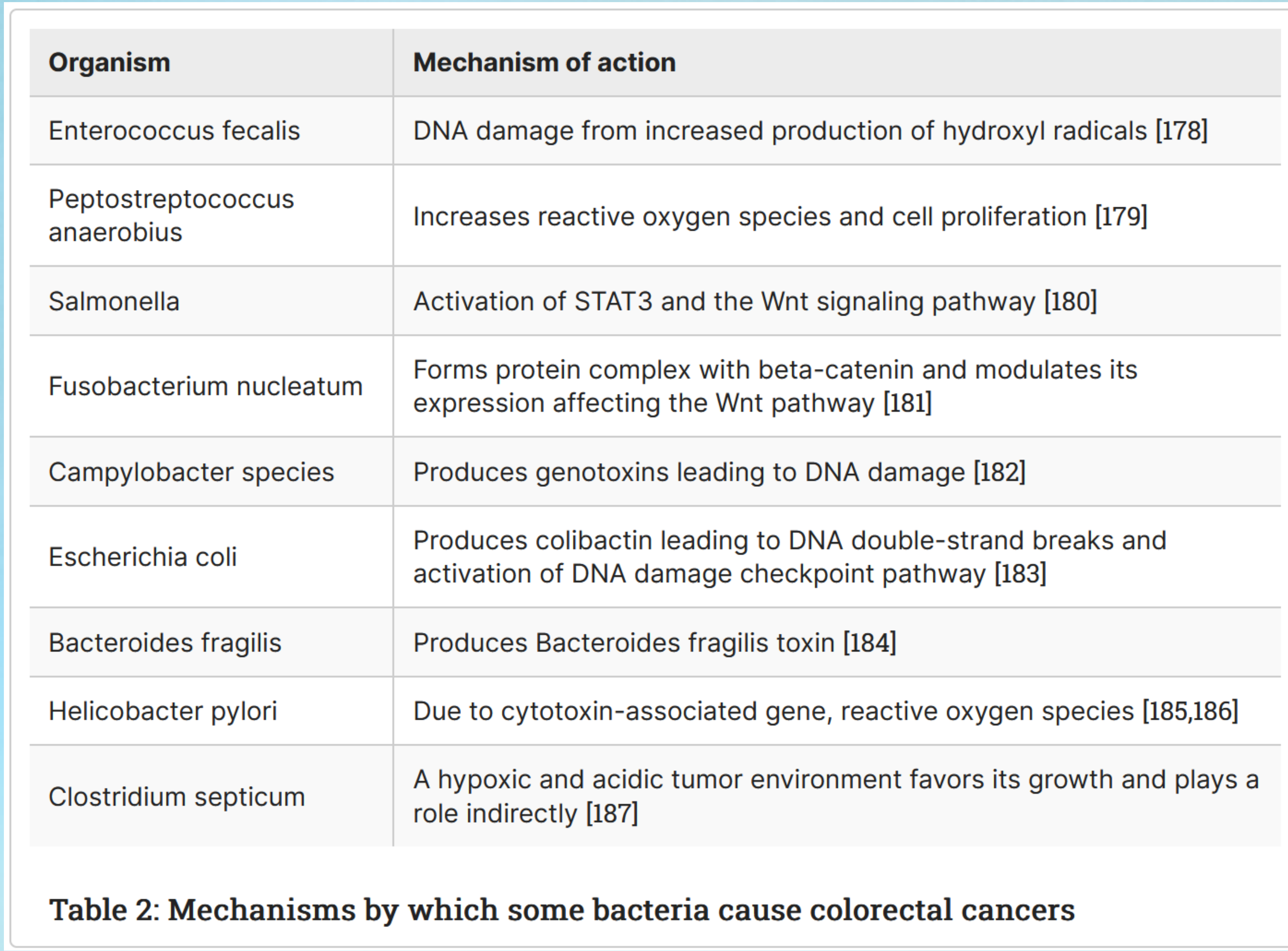
- Probiotics and prebiotics are recommended as part of a multifaceted approach to address these issues by promoting gut harmony, promoting general health, and highlighting the critical need to reduce the deleterious effects of antibiotic therapy on the human microbiota.

# Cancer Connection



| Type of cancer | Cancer microbiome |
|---|---|
| Esophagus | Campylobacter spp. [96,97], Escherichia coli [98] |
| Breast | Streptococcus, Propionibacterium, Escherichia coli, Staphylococcus epidermidis [142,143] |
| Oral | Porphyromonas gingivalis, Fusobacterium nucleatum [165,166] |
| Lung | Granulicatella, Streptococcus, Abiotrophia [167] |
| Liver | Enterococcus, Ruminococcus, Bacteroides, Phascolarctobacterium, and Oscillospira [168] |
| Colon | Fusobacterium nucleatum, Escherichia coli, Bacteroides fragilis, Porphyromonas [169-172] |
| Gall bladder | Fusobacterium nucleatum, Escherichia coli, and Enetrobacter spp. [173] |
| Prostate | Anaerococcus lactolyticus, Varibaculum cambriense, and Propionimicrobium lymphophilium [174] |
| Pancreas | Proteobacteria, Bacteroidetes, and Firmicutes [175-177] |

**Table 1: Examples of specific organisms associated with dysbiosis and cancers**

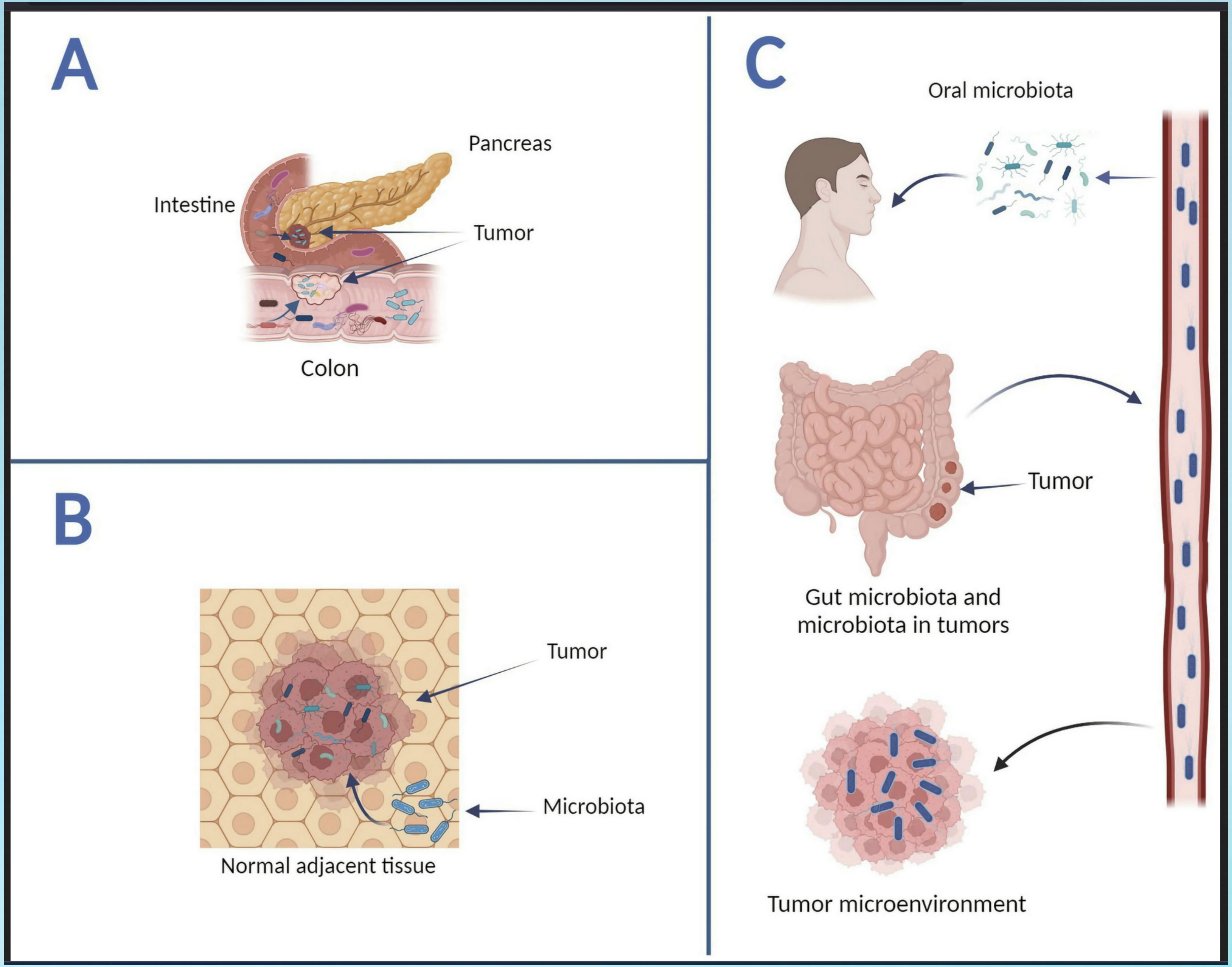


| Organism | Mechanism of action |
|---|---|
| Enterococcus fecalis | DNA damage from increased production of hydroxyl radicals [178] |
| Peptostreptococcus anaerobius | Increases reactive oxygen species and cell proliferation [179] |
| Salmonella | Activation of STAT3 and the Wnt signaling pathway [180] |
| Fusobacterium nucleatum | Forms protein complex with beta-catenin and modulates its expression affecting the Wnt pathway [181] |
| Campylobacter species | Produces genotoxins leading to DNA damage [182] |
| Escherichia coli | Produces colibactin leading to DNA double-strand breaks and activation of DNA damage checkpoint pathway [183] |
| Bacteroides fragilis | Produces Bacteroides fragilis toxin [184] |
| Helicobacter pylori | Due to cytotoxin-associated gene, reactive oxygen species [185,186] |
| Clostridium septicum | A hypoxic and acidic tumor environment favors its growth and plays a role indirectly [187] |

**Table 2: Mechanisms by which some bacteria cause colorectal cancers**

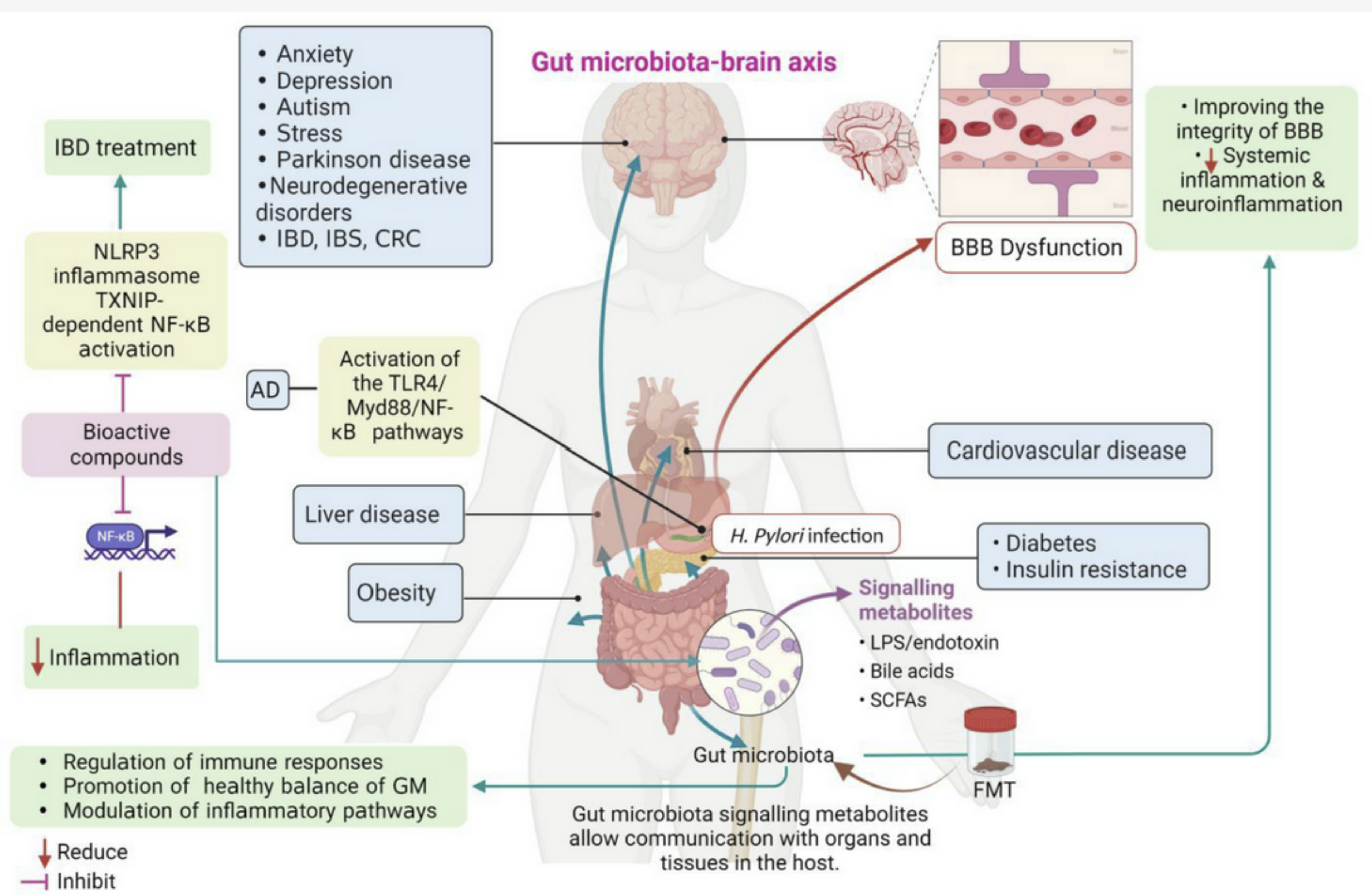
- Studies showing specific microbial signatures in cancers may help us develop specific markers correlating disease severity and prognosis. We can use these signatures to treat cancers with specific organisms that are proved to have anti-cancer or anti-inflammatory properties.

- With the current advances in technology, we can identify microbiota changes associated with different cancers, but significantly more research is needed to develop microbial biomarkers, which can further revolutionize the prevention and help us with early diagnosis of the cancers.


A
Pancreas
Intestine
Tumor
Colon
B
Tumor
Microbiota
Normal adjacent tissue
C
Oral microbiota
Tumor
Gut microbiota and microbiota in tumors
Tumor microenvironment

# Neurological Disorders

# The role of bioactive compounds and Gut microbiota–brain axis (GMBA) in modulating inflammation associated with diseases.



**Gut microbiota-brain axis**

- Anxiety
- Depression
- Autism
- Stress
- Parkinson disease
- Neurodegenerative disorders
- IBD, IBS, CRC

IBD treatment

NLRP3 inflammasome TXNIP-dependent NF-κB activation

Bioactive compounds

↓ Inflammation

AD

Activation of the TLR4/ Myd88/NF-κB pathways

Liver disease

Obesity

BBB Dysfunction

- Improving the integrity of BBB
- ↓ Systemic inflammation & neuroinflammation

Cardiovascular disease

*H. Pylori* infection

- Diabetes
- Insulin resistance

**Signalling metabolites**

- LPS/endotoxin
- Bile acids
- SCFAs

Gut microbiota

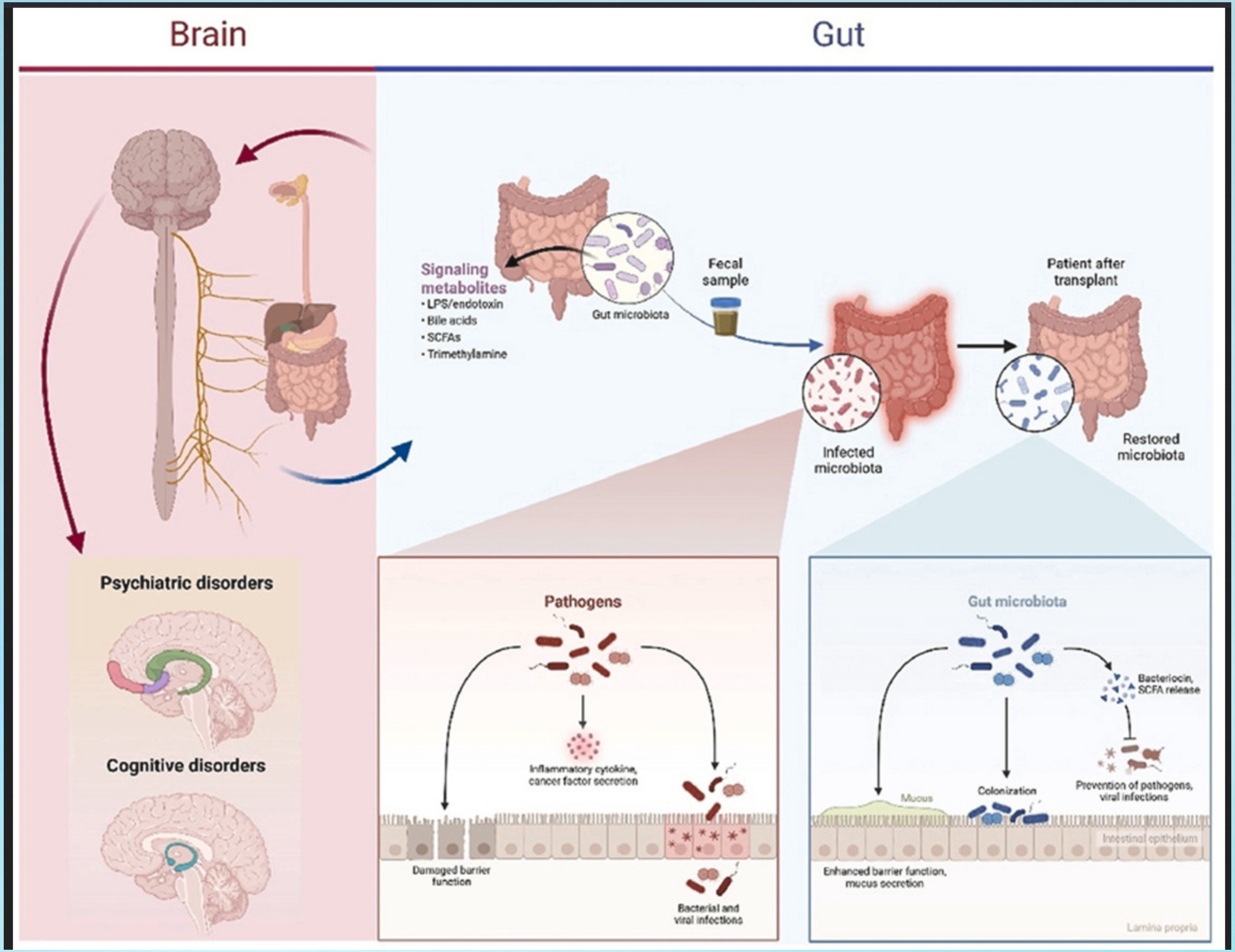
FMT

- Regulation of immune responses
- Promotion of healthy balance of GM
- Modulation of inflammatory pathways

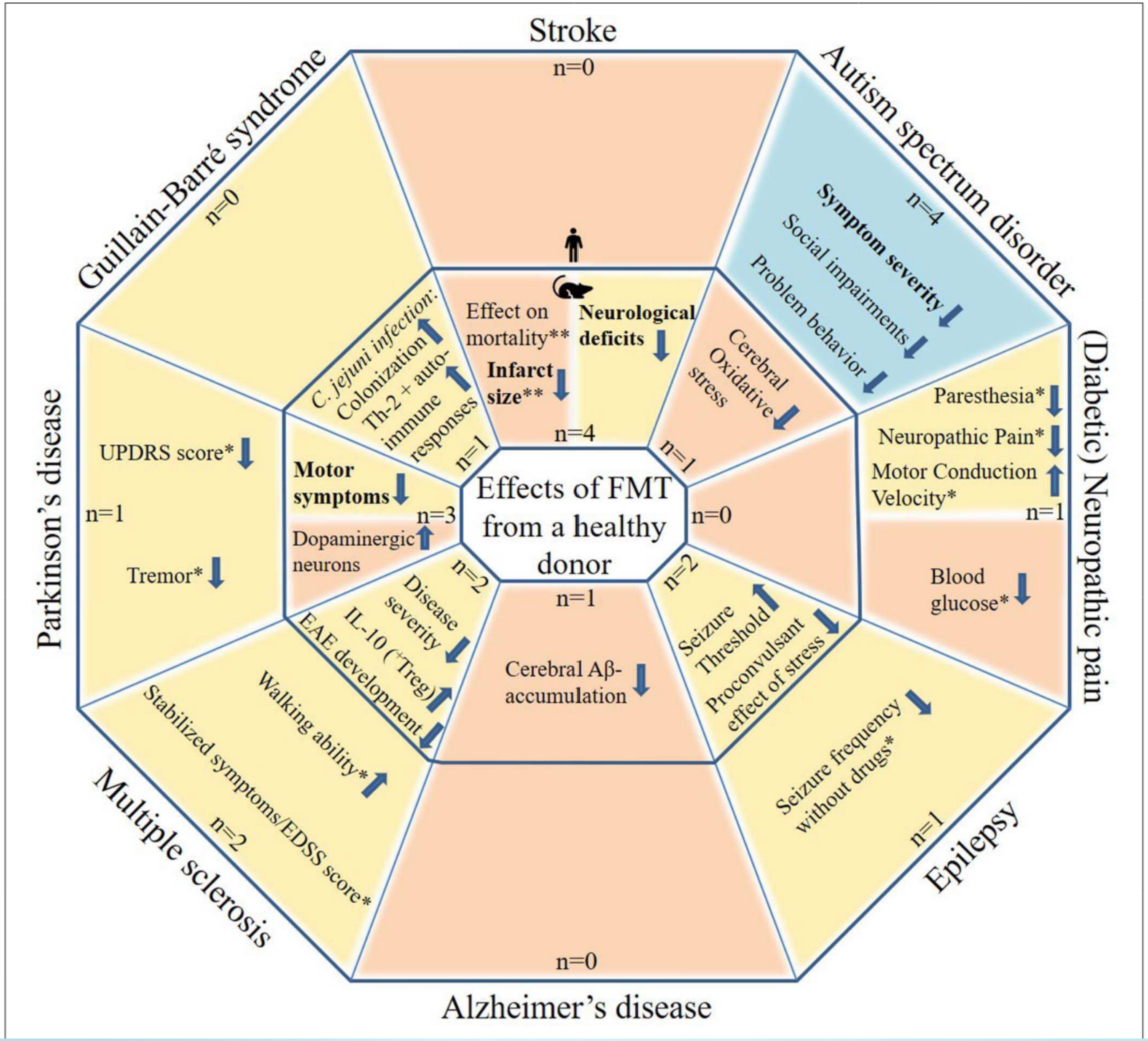
Gut microbiota signalling metabolites allow communication with organs and tissues in the host.

↓ Reduce

⊣ Inhibit


Brain
Gut
Signaling metabolites
• LPS/endotoxin
• Bile acids
• SCFAs
• Trimethylamine
Gut microbiota
Fecal sample
Patient after transplant
Infected microbiota
Restored microbiota
Psychiatric disorders
Cognitive disorders
Pathogens
Inflammatory cytokine, cancer factor secretion
Damaged barrier function
Bacterial and viral infections
Gut microbiota
Bacteriocin, SCFA release
Mucus
Colonization
Prevention of pathogens, viral infections
Intestinal epithelium
Enhanced barrier function, mucus secretion
Lamina propria

Vendrik et al. FMT in Neurological Disorders



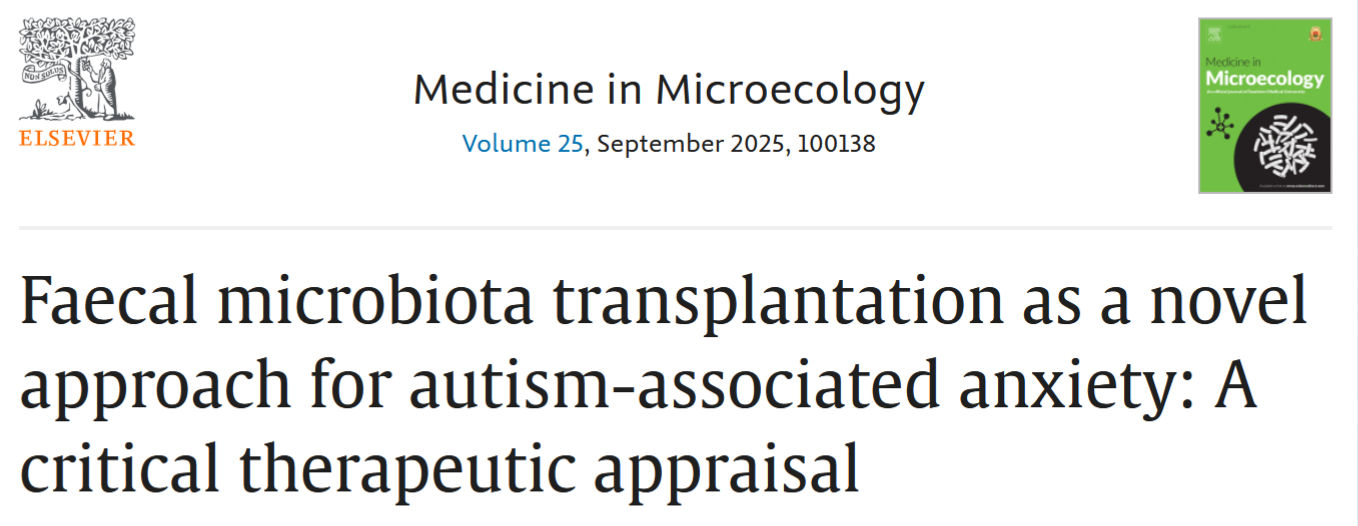
Vendrik et al.

FMT in Neurological Disorders

Conclusions:

- Preliminary literature suggests that FMT may be a promising treatment option for several neurological disorders.
- However, available evidence is still scanty and some contrasting results were observed.
- A limited number of studies in humans have been performed or are ongoing, while for some disorders only animal experiments havebeen conducted.

frontiers in Cellular and Infection Microbiology
REVIEW
published: 24 March 2020
doi: 10.3389/fcimb.2020.00098



ELSEVIER

Medicine in Microecology

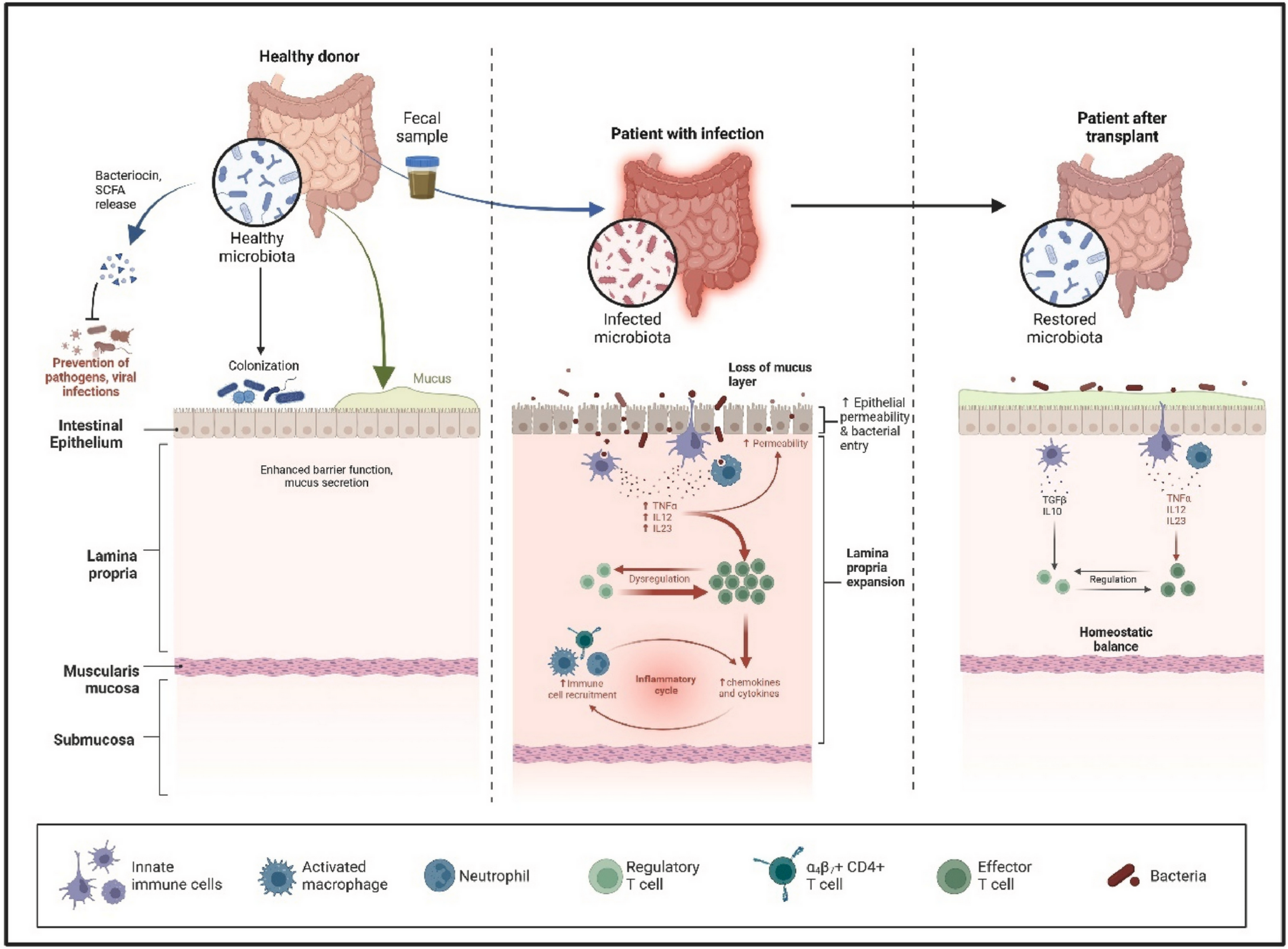
Volume 25, September 2025, 100138

## Faecal microbiota transplantation as a novel approach for autism-associated anxiety: A critical therapeutic appraisal

••Gut microbiota dysregulation contributes to ASD associated anxiety.

••FMT regulate GBA and neurotransmitter signalling to improve anxiety in ASD.

••FMT offers new therapeutic approach for cognitive and social impairment in ASD.

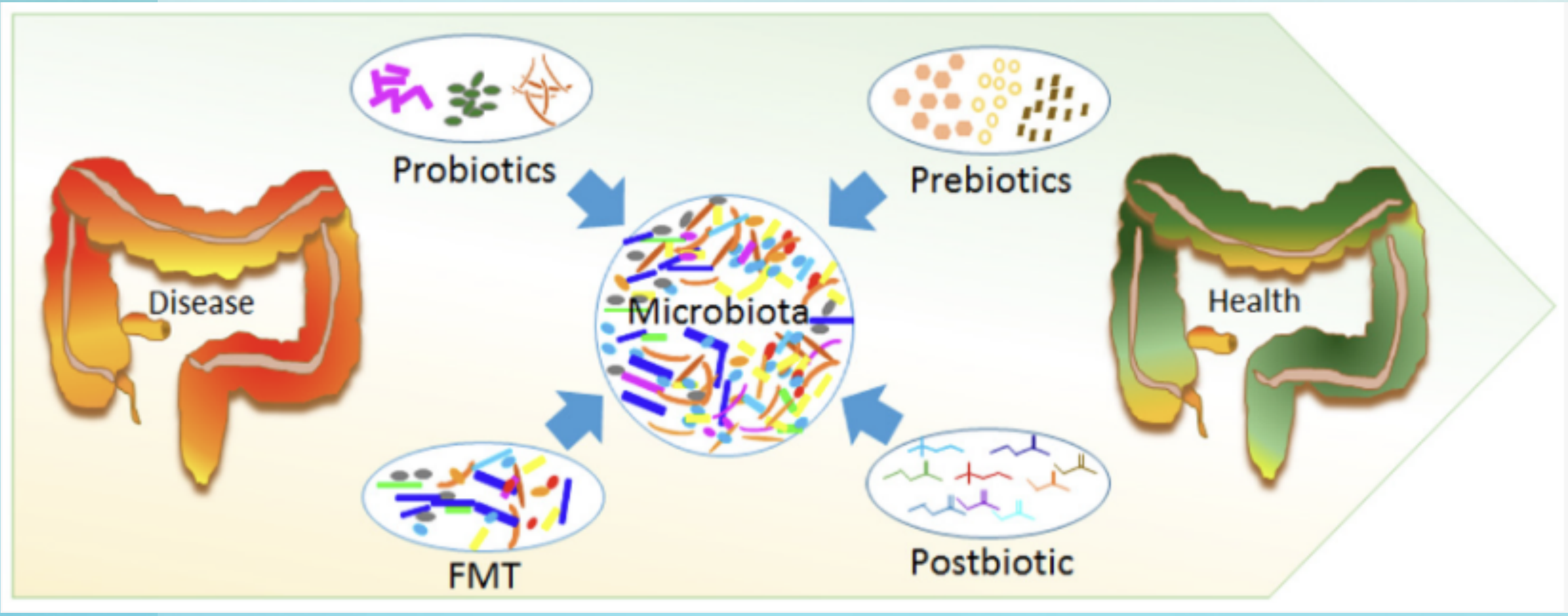


# Mechanisms of FMT in four areas:

1. Replenishing beneficial bacteria to restore microbial balance,
2. Enhancing scfa production to improve metabolism,
3. Reducing gut permeability to strengthen the gut lining and gut-brain signalling,
4. Influencing bile acid metabolism to optimize metabolic pathways.

Collectively, these mechanisms contribute to overall health restoration

# Implication of this Knowledge



The composition of the gut microbiota continues to shift based on diet, disease state, genetics, and medication intake

Several studies have shown that many diets, including plant-based, high-fat, and low-fat, change the microbiota composition significantly

A crucial part of the dietary fiber makeup in gut microbiota is that they produce metabolites, of which short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are more noteworthy

Vernocchi, P.; Del Chierico, F.; Putignani, L. Gut Microbiota Metabolism and Interaction with Food Components. *Int. J. Mol. Sci.* **2020**, *21*, 3688. https://doi.org/10.3390/ijms21103688

The **Mediterranean diet**, which is high in plant-based foods, low in animal protein and saturated fat, and high in fiber and omega-3 fatty acids, was linked to higher concentrations of SCFA, Prevotella, and Firmicutes, known to break down fiber.

- In clinical trials, a reduced number of Bifidobacteria was found to increase endotoxemia in high-fat diet-fed mice.
- With the supplementation of prebiotics, this was found to be reversed. In the **plant-derived foods group**, an increased synthesis of amylase, glutamate, and riboflavin was observed .
- Intake of **animal-based foods** leads to the adaptation of gut microbial function towards improved catabolic processes like the degradation of glycans and amino acids

Beam A, Clinger E, Hao L: Effect of diet and dietary components on the composition of the gut microbiota . Nutrients. 2021, 13:10.3390/nu13082795

**Fecal microbiota transplant, a treatment that dates back over 1000 years to Chinese practitioners and was first published as a modern therapeutic intervention in 1958, is the process by which a fecal sample from a "healthy" individual is transplanted into the gut via enema, nasogastric tube or colonoscopy of a diseased patient.**

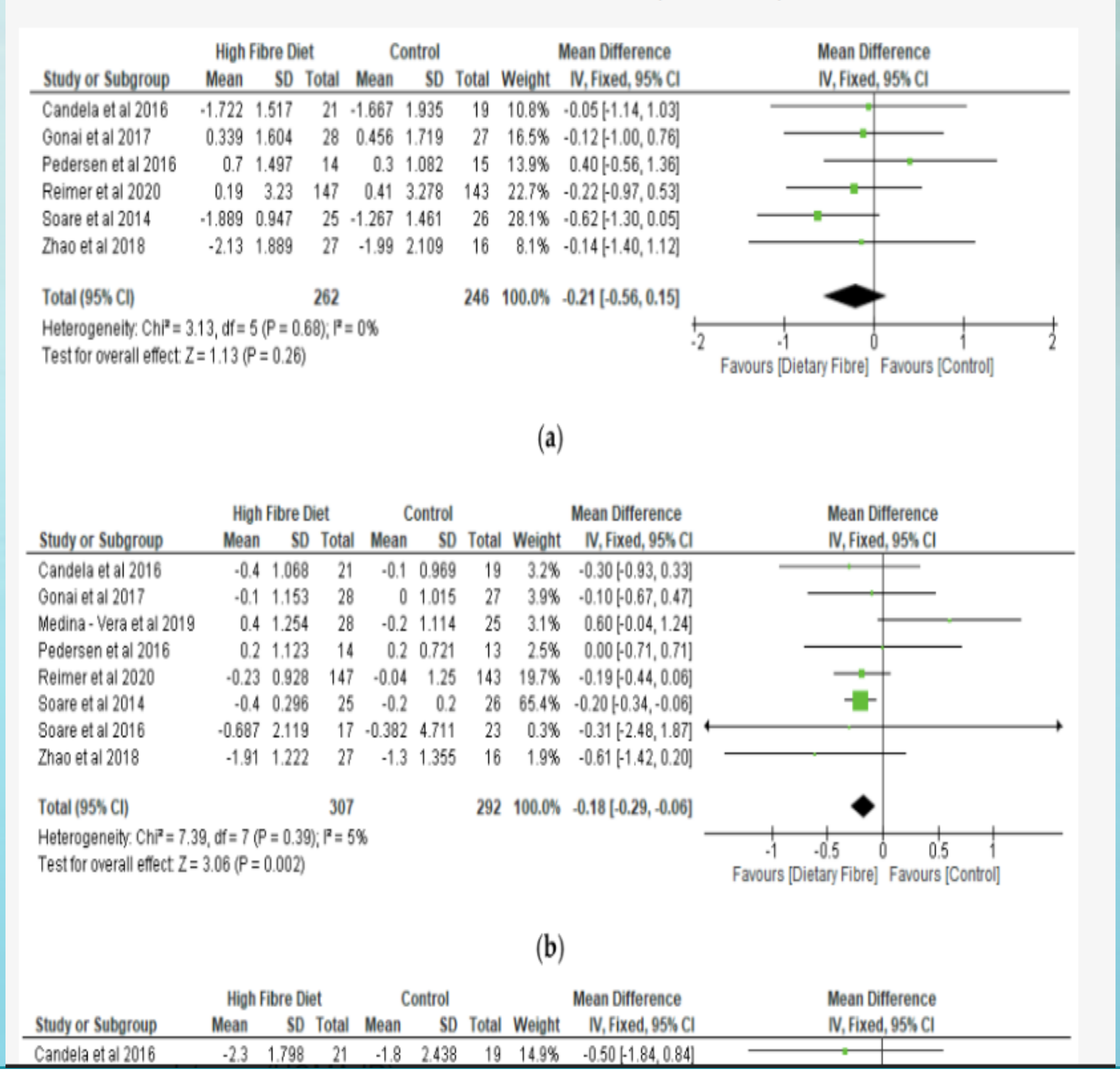
**This is a new era of "organ" transplant!**

Fecal microbiota transplant from lean healthy donors has also found to be successful in improving insulin sensitivity in men with metabolic syndrome

# The effect of dietary fibre on fasting blood glucose , Hb1ac & (HOMA-IR).

Dysbiosis of the gut microbiota is known to affect the production of SCFA, altering the bile acid profile and the endocannabinoid system, causing a reduction in GLP-1, GLP-2 (glucagon-like-peptide 1,2) and PYY (peptide YY),

An impaired gut barrier and pave the way for a cascade of events that lead to decreased insulin sensitivity, increased ongoing inflammation, more oxidative stress, increased steatosis, and increased fat mass



| | High Fibre Diet | | | Control | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI |
| Candela et al 2016 | -1.722 | 1.517 | 21 | -1.667 | 1.935 | 19 | 10.8% | -0.05 [-1.14, 1.03] |
| Gonai et al 2017 | 0.339 | 1.604 | 28 | 0.456 | 1.719 | 27 | 16.5% | -0.12 [-1.00, 0.76] |
| Pedersen et al 2016 | 0.7 | 1.497 | 14 | 0.3 | 1.082 | 15 | 13.9% | 0.40 [-0.56, 1.36] |
| Reimer et al 2020 | 0.19 | 3.23 | 147 | 0.41 | 3.278 | 143 | 22.7% | -0.22 [-0.97, 0.53] |
| Soare et al 2014 | -1.889 | 0.947 | 25 | -1.267 | 1.461 | 26 | 28.1% | -0.62 [-1.30, 0.05] |
| Zhao et al 2018 | -2.13 | 1.889 | 27 | -1.99 | 2.109 | 16 | 8.1% | -0.14 [-1.40, 1.12] |
| **Total (95% CI)** | | | **262** | | | **246** | **100.0%** | **-0.21 [-0.56, 0.15]** |

Heterogeneity: Chi² = 3.13, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

(a)

| | High Fibre Diet | | | Control | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI |
| Candela et al 2016 | -0.4 | 1.068 | 21 | -0.1 | 0.969 | 19 | 3.2% | -0.30 [-0.93, 0.33] |
| Gonai et al 2017 | -0.1 | 1.153 | 28 | 0 | 1.015 | 27 | 3.9% | -0.10 [-0.67, 0.47] |
| Medina - Vera et al 2019 | 0.4 | 1.254 | 28 | -0.2 | 1.114 | 25 | 3.1% | 0.60 [-0.04, 1.24] |
| Pedersen et al 2016 | 0.2 | 1.123 | 14 | 0.2 | 0.721 | 13 | 2.5% | 0.00 [-0.71, 0.71] |
| Reimer et al 2020 | -0.23 | 0.928 | 147 | -0.04 | 1.25 | 143 | 19.7% | -0.19 [-0.44, 0.06] |
| Soare et al 2014 | -0.4 | 0.296 | 25 | -0.2 | 0.2 | 26 | 65.4% | -0.20 [-0.34, -0.06] |
| Soare et al 2016 | -0.687 | 2.119 | 17 | -0.382 | 4.711 | 23 | 0.3% | -0.31 [-2.48, 1.87] |
| Zhao et al 2018 | -1.91 | 1.222 | 27 | -1.3 | 1.355 | 16 | 1.9% | -0.61 [-1.42, 0.20] |
| **Total (95% CI)** | | | **307** | | | **292** | **100.0%** | **-0.18 [-0.29, -0.06]** |

Heterogeneity: Chi² = 7.39, df = 7 (P = 0.39); I² = 5%
Test for overall effect: Z = 3.06 (P = 0.002)

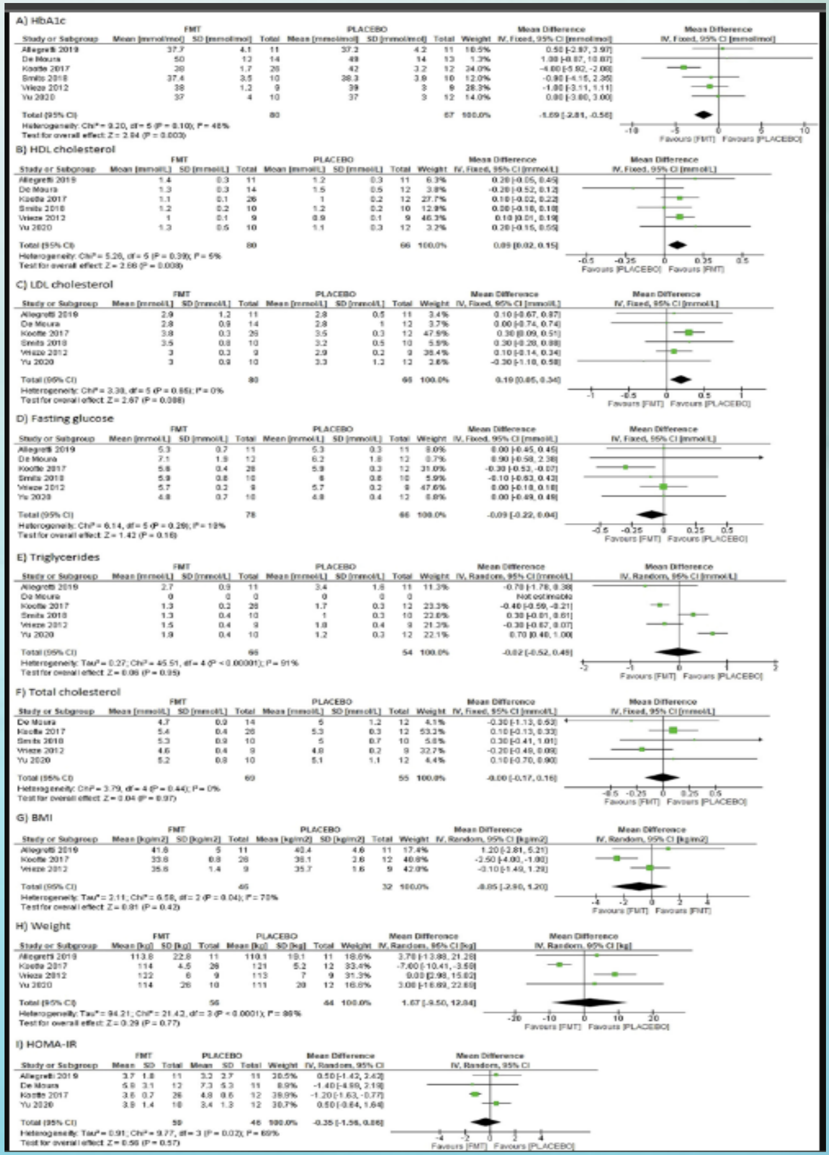
(b)

| | High Fibre Diet | | | Control | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI |
| Candela et al 2016 | -2.3 | 1.798 | 21 | -1.8 | 2.438 | 19 | 14.9% | -0.50 [-1.84, 0.84] |

Ojo, O.; Feng, Q.-Q.; Ojo, O.O.; Wang, X.-H. The Role of Dietary Fibre in Modulating Gut Microbiota Dysbiosis in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Nutrients* **2020**, *12*, 3239. https://doi.org/10.3390/nu12113239

# A very innovative way of targeting to change the composition of the intestinal microbiota: FMTs

The very possible observations from individuals tolerating the oral formulations and fecal microbiota transplant therapy done so far and the changes observed in the intestinal microbiome seem promising and revolutionary

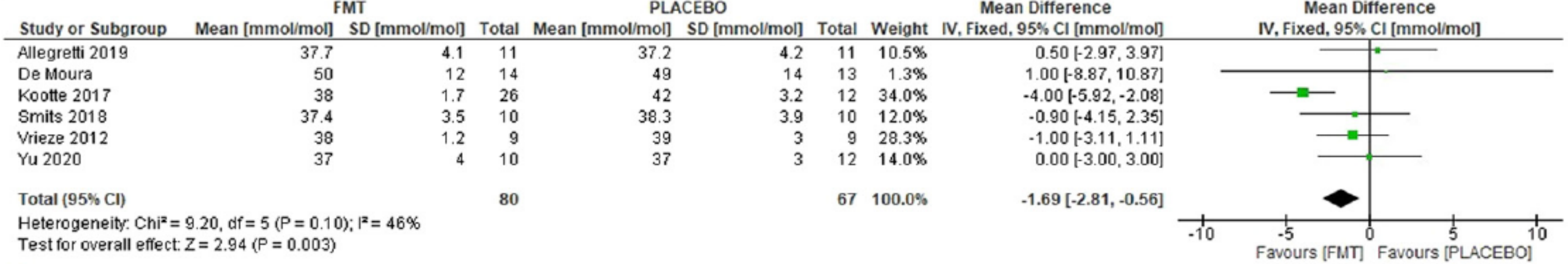


Proença IM, Allegretti JR, Bernardo WM, et al.: Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials. Nutr Res. 2020, 83:1-14. 10.1016/j.nutres.2020.06.018

# Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials

Igor M. Proença,Jessica R. Allegretti, Wanderley M. Bernardo, Diogo T.H. de Moura,Alberto M. Ponte Neto, Carolina O. Matsubayashi a, Marcelo M. Flor a, Ana P.S.T. Kotinda a,Eduardo G.H. de Moura

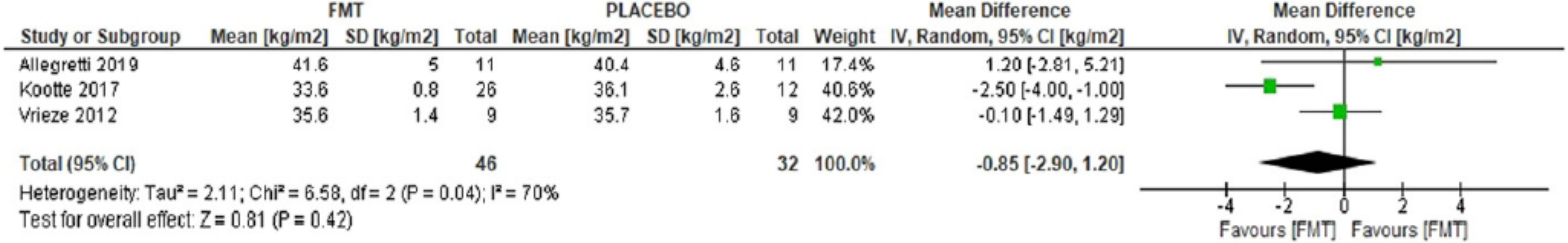
## HbA1c



| | FMT | | | PLACEBO | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean [mmol/mol] | SD [mmol/mol] | Total | Mean [mmol/mol] | SD [mmol/mol] | Total | Weight | IV, Fixed, 95% CI [mmol/mol] |
| Allegretti 2019 | 37.7 | 4.1 | 11 | 37.2 | 4.2 | 11 | 10.5% | 0.50 [-2.97, 3.97] |
| De Moura | 50 | 12 | 14 | 49 | 14 | 13 | 1.3% | 1.00 [-8.87, 10.87] |
| Kootte 2017 | 38 | 1.7 | 26 | 42 | 3.2 | 12 | 34.0% | -4.00 [-5.92, -2.08] |
| Smits 2018 | 37.4 | 3.5 | 10 | 38.3 | 3.9 | 10 | 12.0% | -0.90 [-4.15, 2.35] |
| Vrieze 2012 | 38 | 1.2 | 9 | 39 | 3 | 9 | 28.3% | -1.00 [-3.11, 1.11] |
| Yu 2020 | 37 | 4 | 10 | 37 | 3 | 12 | 14.0% | 0.00 [-3.00, 3.00] |
| **Total (95% CI)** | | | **80** | | | **67** | **100.0%** | **-1.69 [-2.81, -0.56]** |

Heterogeneity: Chi² = 9.20, df = 5 (P = 0.10); I² = 46%
Test for overall effect: Z = 2.94 (P = 0.003)

## BMI



| | FMT | | | PLACEBO | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean [kg/m2] | SD [kg/m2] | Total | Mean [kg/m2] | SD [kg/m2] | Total | Weight | IV, Random, 95% CI [kg/m2] |
| Allegretti 2019 | 41.6 | 5 | 11 | 40.4 | 4.6 | 11 | 17.4% | 1.20 [-2.81, 5.21] |
| Kootte 2017 | 33.6 | 0.8 | 26 | 36.1 | 2.6 | 12 | 40.6% | -2.50 [-4.00, -1.00] |
| Vrieze 2012 | 35.6 | 1.4 | 9 | 35.7 | 1.6 | 9 | 42.0% | -0.10 [-1.49, 1.29] |
| **Total (95% CI)** | | | **46** | | | **32** | **100.0%** | **-0.85 [-2.90, 1.20]** |

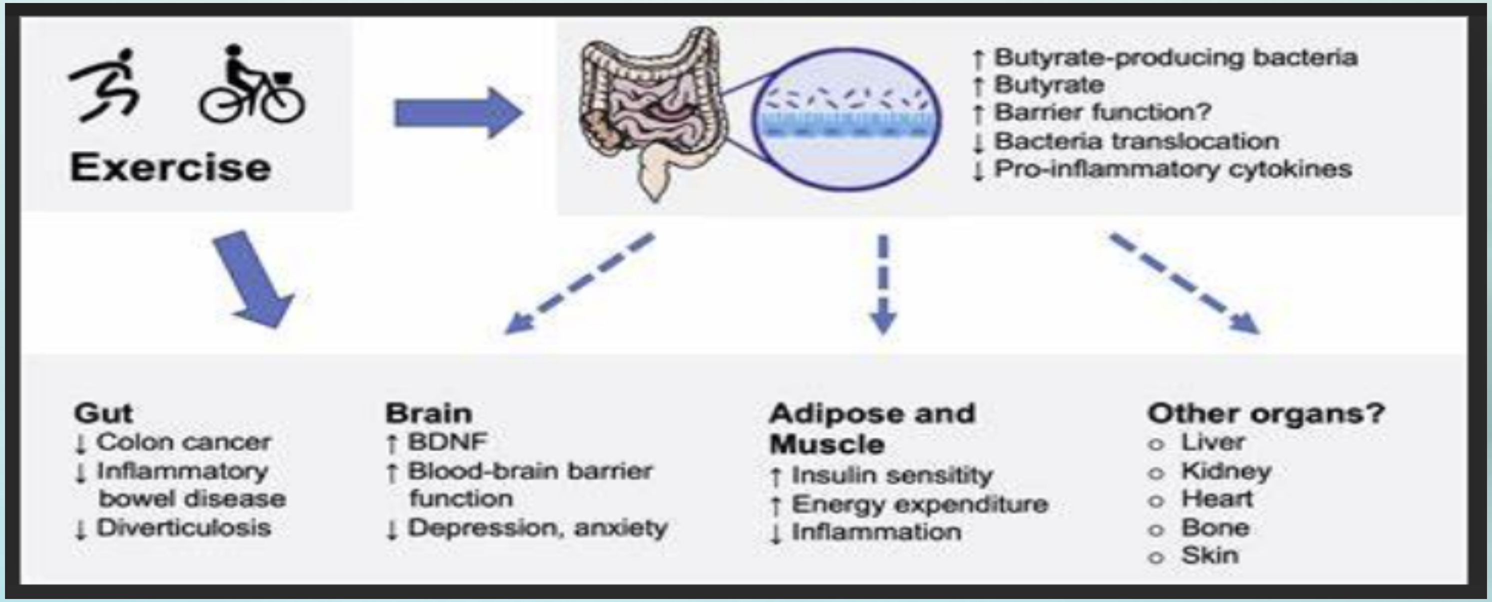
Heterogeneity: Tau² = 2.11; Chi² = 6.58, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 0.81 (P = 0.42)

NUTRITION RESEARCH 2020

# Exercise

# T2DM

# Gut Microbiota



**Exercise**

↑ Butyrate-producing bacteria
↑ Butyrate
↑ Barrier function?
↓ Bacteria translocation
↓ Pro-inflammatory cytokines

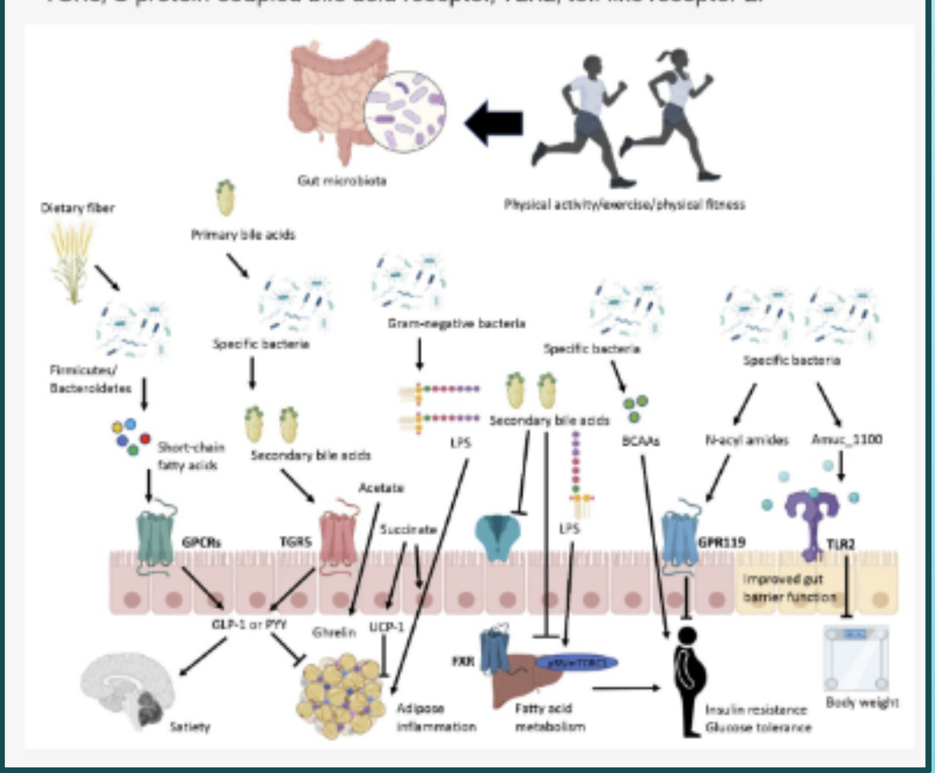
**Gut**
↓ Colon cancer
↓ Inflammatory bowel disease
↓ Diverticulosis

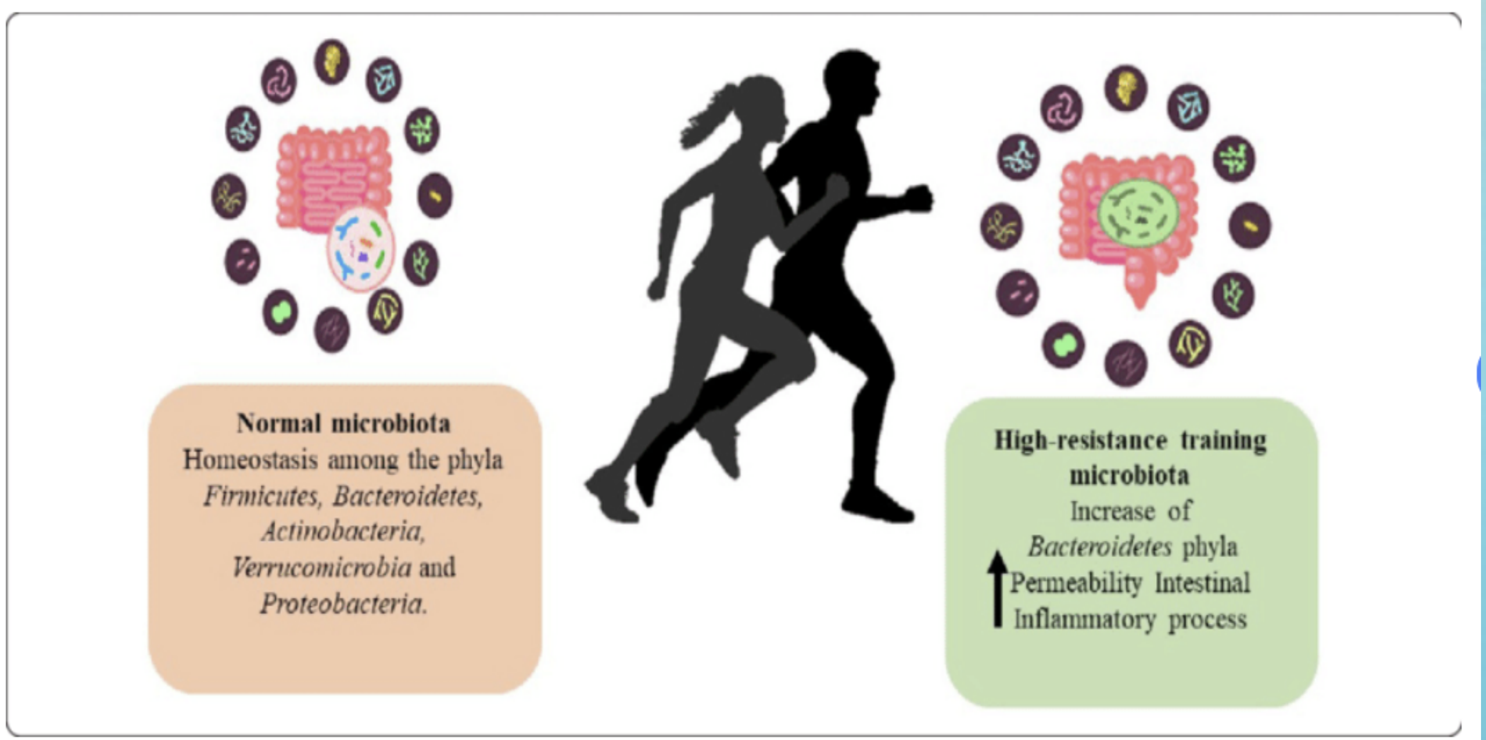
**Brain**
↑ BDNF
↑ Blood-brain barrier function
↓ Depression, anxiety

**Adipose and Muscle**
↑ Insulin sensitivity
↑ Energy expenditure
↓ Inflammation

**Other organs?**
- ○ Liver
- ○ Kidney
- ○ Heart
- ○ Bone
- ○ Skin

TGR5, G-protein-coupled bile acid receptor; TLR2, toll-like receptor 2.



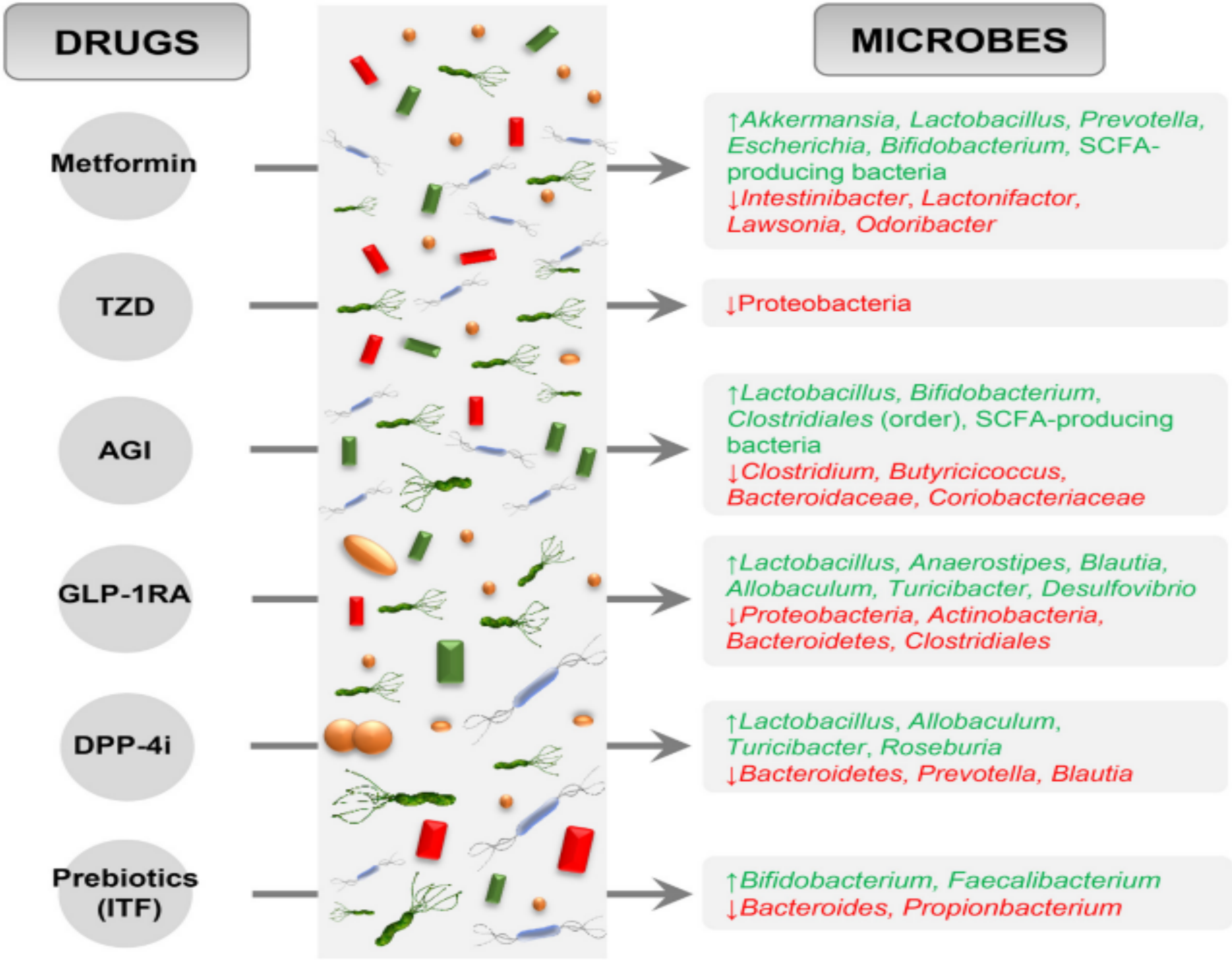


**Normal microbiota**
Homeostasis among the phyla *Firmicutes, Bacteroidetes, Actinobacteria, Verrucomicrobia* and *Proteobacteria.*

**High-resistance training microbiota**
Increase of *Bacteroidetes* phyla
↑ Permeability Intestinal
Inflammatory process

# Effects of antidiabetic drugs on the relative abundance of gut microbes.

A. Whang et al. / EBioMedicine 39 (2019) 591–602



**DRUGS**

**MICROBES**

**Metformin** → ↑*Akkermansia*, *Lactobacillus*, *Prevotella*, *Escherichia*, *Bifidobacterium*, SCFA-producing bacteria
↓*Intestinibacter*, *Lactonifactor*, *Lawsonia*, *Odoribacter*

**TZD** → ↓Proteobacteria

**AGI** → ↑*Lactobacillus*, *Bifidobacterium*, *Clostridiales* (order), SCFA-producing bacteria
↓*Clostridium*, *Butyricicoccus*, *Bacteroidaceae*, *Coriobacteriaceae*

**GLP-1RA** → ↑*Lactobacillus*, *Anaerostipes*, *Blautia*, *Allobaculum*, *Turicibacter*, *Desulfovibrio*
↓*Proteobacteria*, *Actinobacteria*, *Bacteroidetes*, *Clostridiales*

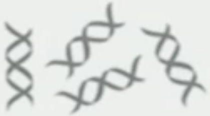
**DPP-4i** → ↑*Lactobacillus*, *Allobaculum*, *Turicibacter*, *Roseburia*
↓*Bacteroidetes*, *Prevotella*, *Blautia*

**Prebiotics (ITF)** → ↑*Bifidobacterium*, *Faecalibacterium*
↓*Bacteroides*, *Propionbacterium*

# Diagnostic Implications

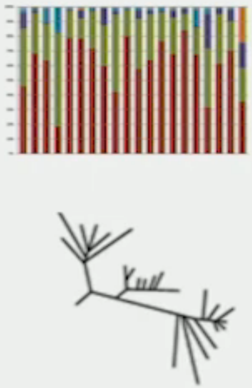
# Enabling Tools To Interrogate Microbial Dark Matter

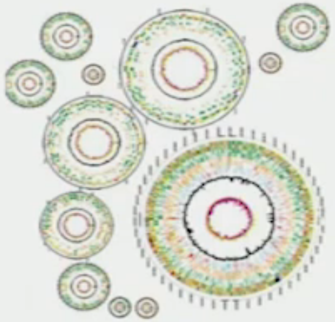
**DNA**



16S rRNA
ITS2

Shotgun metagenomics



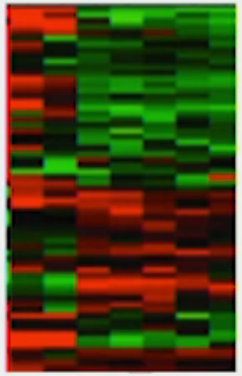


Composition

Functional capacity

**RNA**

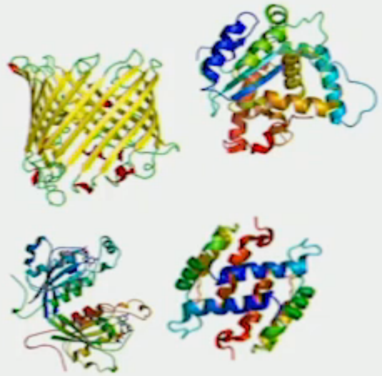
Metatranscriptomics



Gene expression

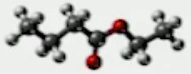
**Protein**

Metaproteomics

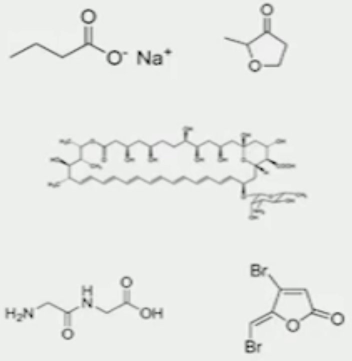


Catalytic functions

**Metabolites**



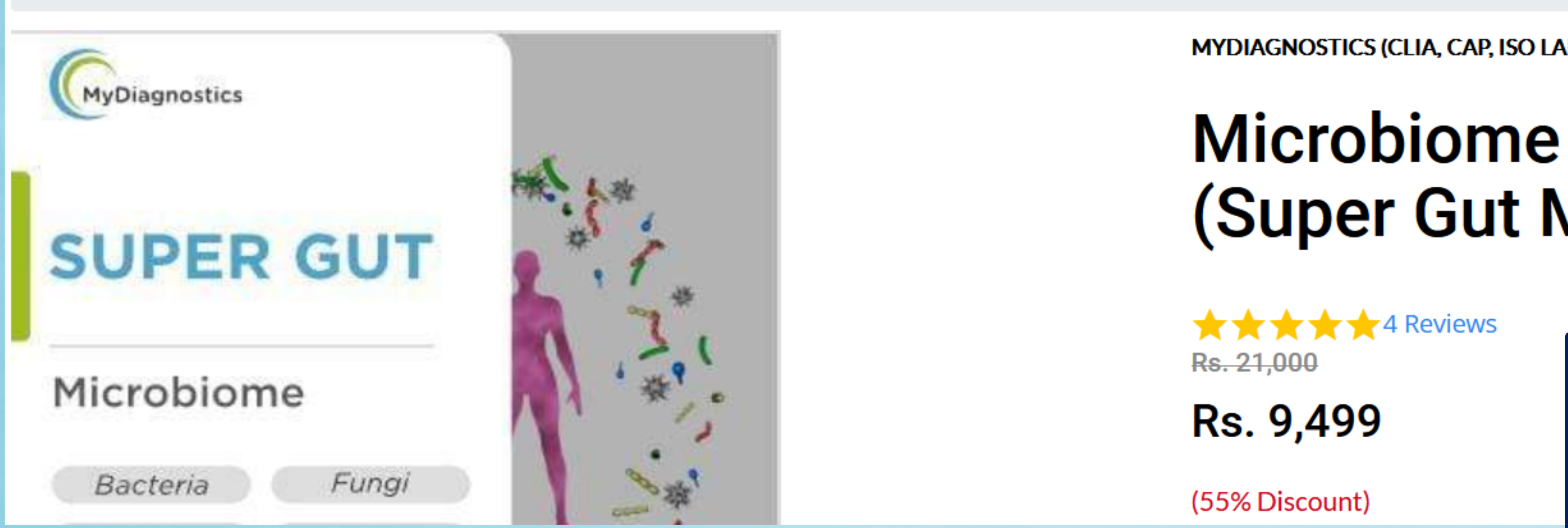
Metabolomics



Metabolic activity

Next-generation sequencing platforms

Untargeted/targeted Mass spectrometry



**MYDIAGNOSTICS (CLIA, CAP, ISO LAB)**

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★★★★☆ (66)

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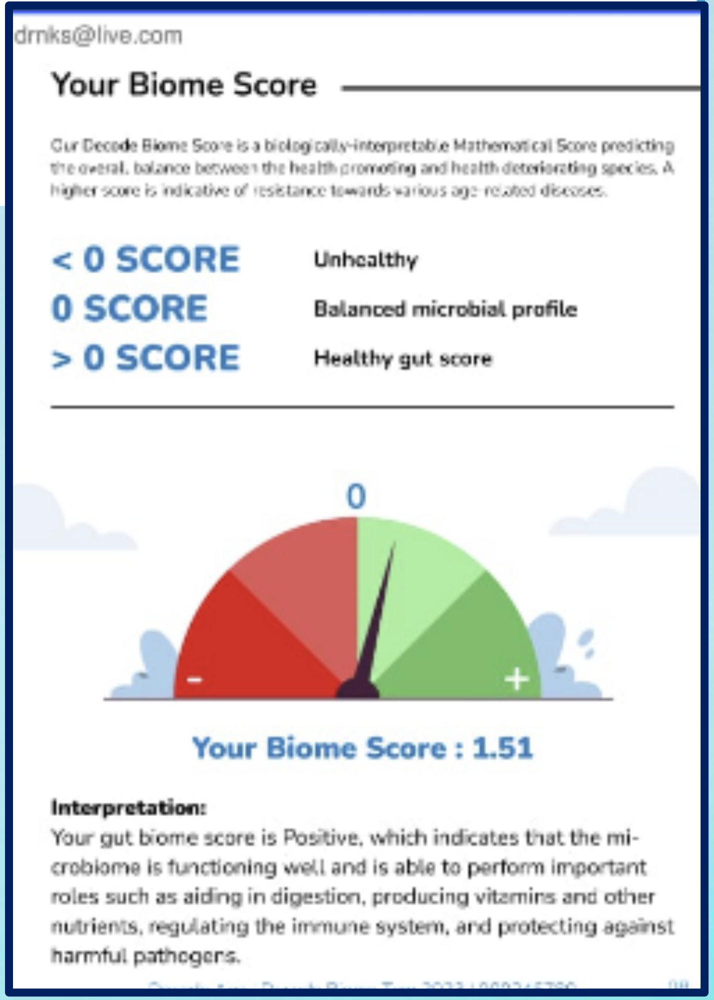
**Benefits**



drnks@live.com

## Your Biome Score

Our Decode Biome Score is a biologically-interpretable Mathematical Score predicting the overall balance between the health promoting and health deteriorating species. A higher score is indicative of resistance towards various age related diseases.

| | |
|---|---|
| < 0 SCORE | Unhealthy |
| 0 SCORE | Balanced microbial profile |
| > 0 SCORE | Healthy gut score |

**Your Biome Score : 1.51**

**Interpretation:**
Your gut biome score is Positive, which indicates that the microbiome is functioning well and is able to perform important roles such as aiding in digestion, producing vitamins and other nutrients, regulating the immune system, and protecting against harmful pathogens.

A positive correlation between trimethylamine N-oxide in plasma at birth (TMAO) and the possible increased risk of major cardiovascular adverse events has been suggested;

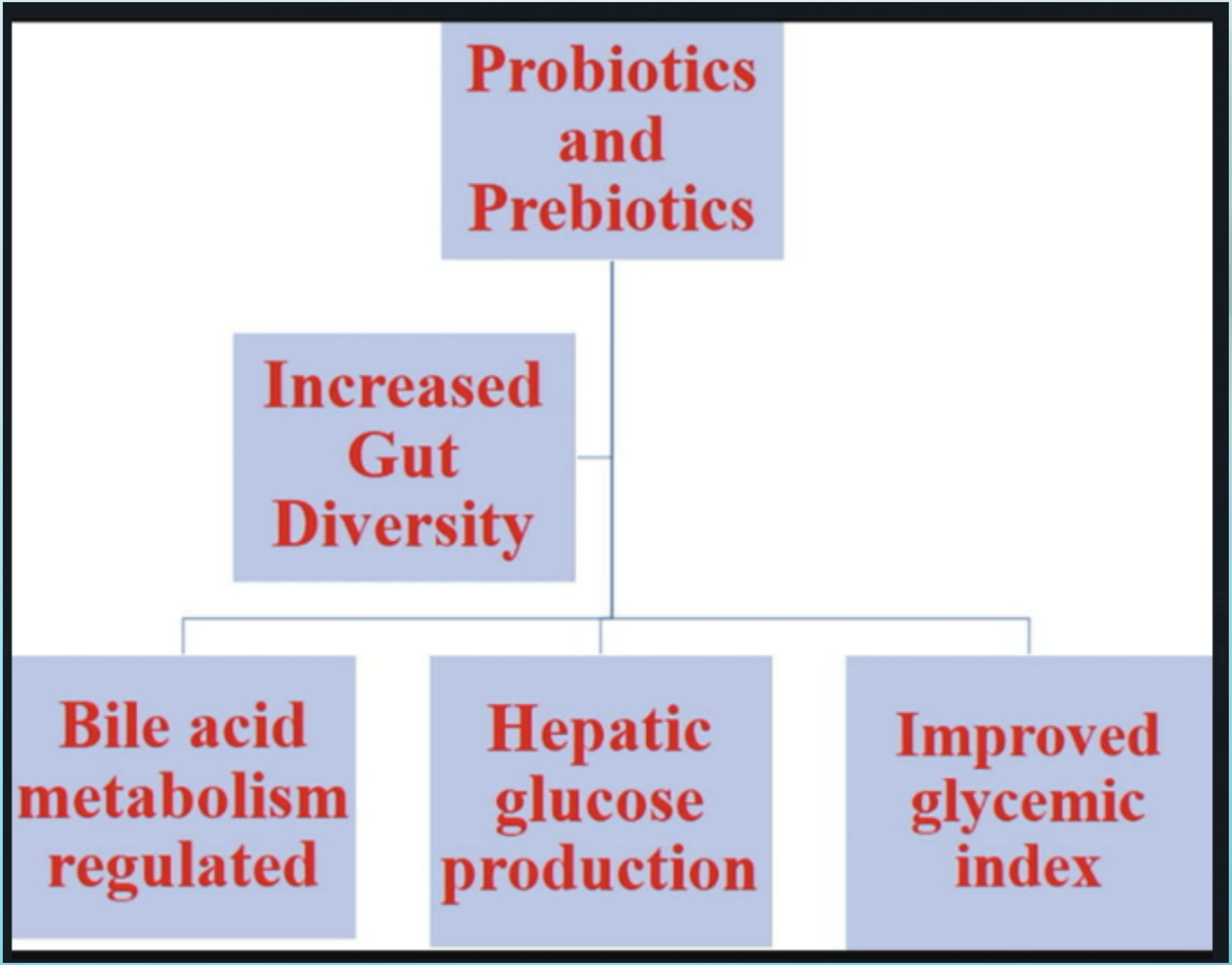
The value of diagnosing TMAO levels in blood in cardiovascular diseases is questionable.

The concentration of TMAO in the blood may depend on a few factors, including diet, intestinal microbial activity, GBB permeability to TMA, liver and TMA oxidation, and TMA and TMAO excretion

The plasma level of TMAO in the human organism is in the range of 0.5-10 µmol/L.

# What we can do in 2025

## Therapeutic Implications



Probiotics and Prebiotics

Increased Gut Diversity

Bile acid metabolism regulated

Hepatic glucose production

Improved glycemic index

# Possibility of intervention on gut microbiome proposed as a potential therapeutic strategy

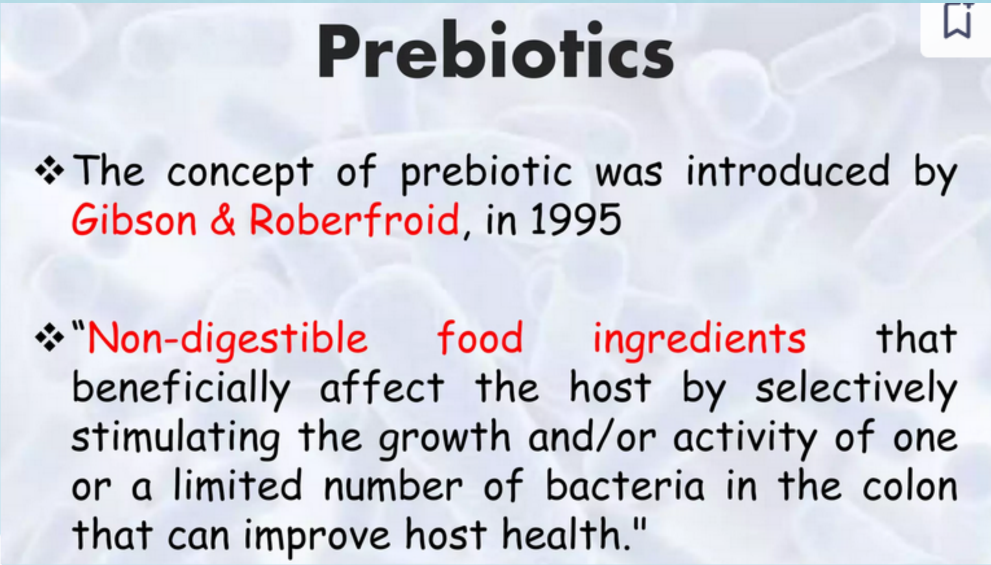
3 things
Are
Important

1. Dietary modifications
2. Treatment with Probiotics, Prebiotics & Postbiotics
3. Faecal transplantation

Prebiotics promote the growth or action of beneficial microbes and include fructooligosaccharides or galactooligosaccharides, lactulose, and nondigestible carbohydrates (eg, inulin, cellulose, and pectin) .

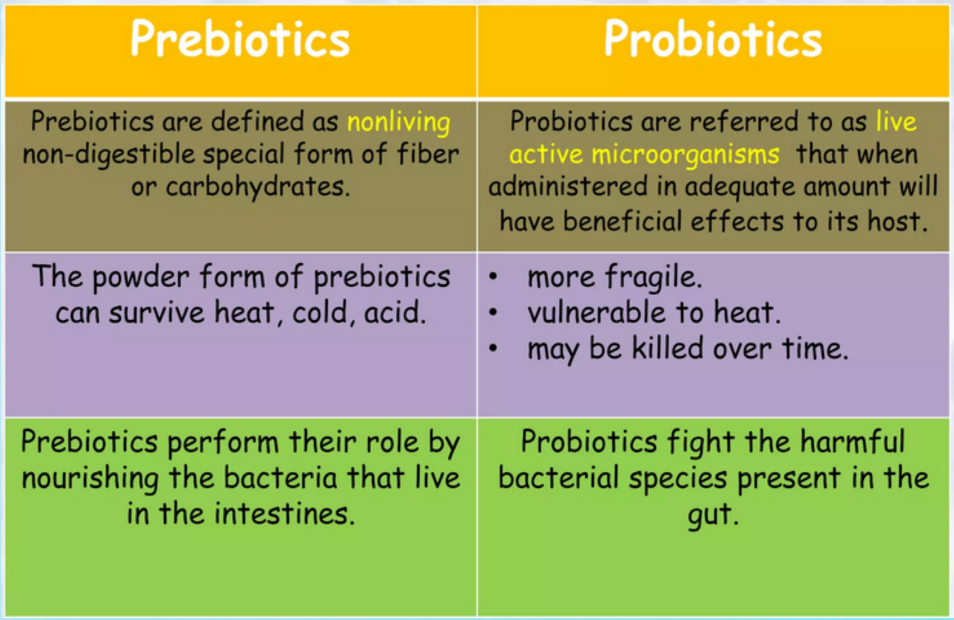
Probiotics are live microorganisms, predominantly commensal gut bacteria such
as Lactobacillus and Bifidobacterium

Postbiotics are the byproducts of the metabolic processes of probiotic bacteria. It has been reported that GABA improves glucoseintolerance, b-cell mass, and inflammatory response .



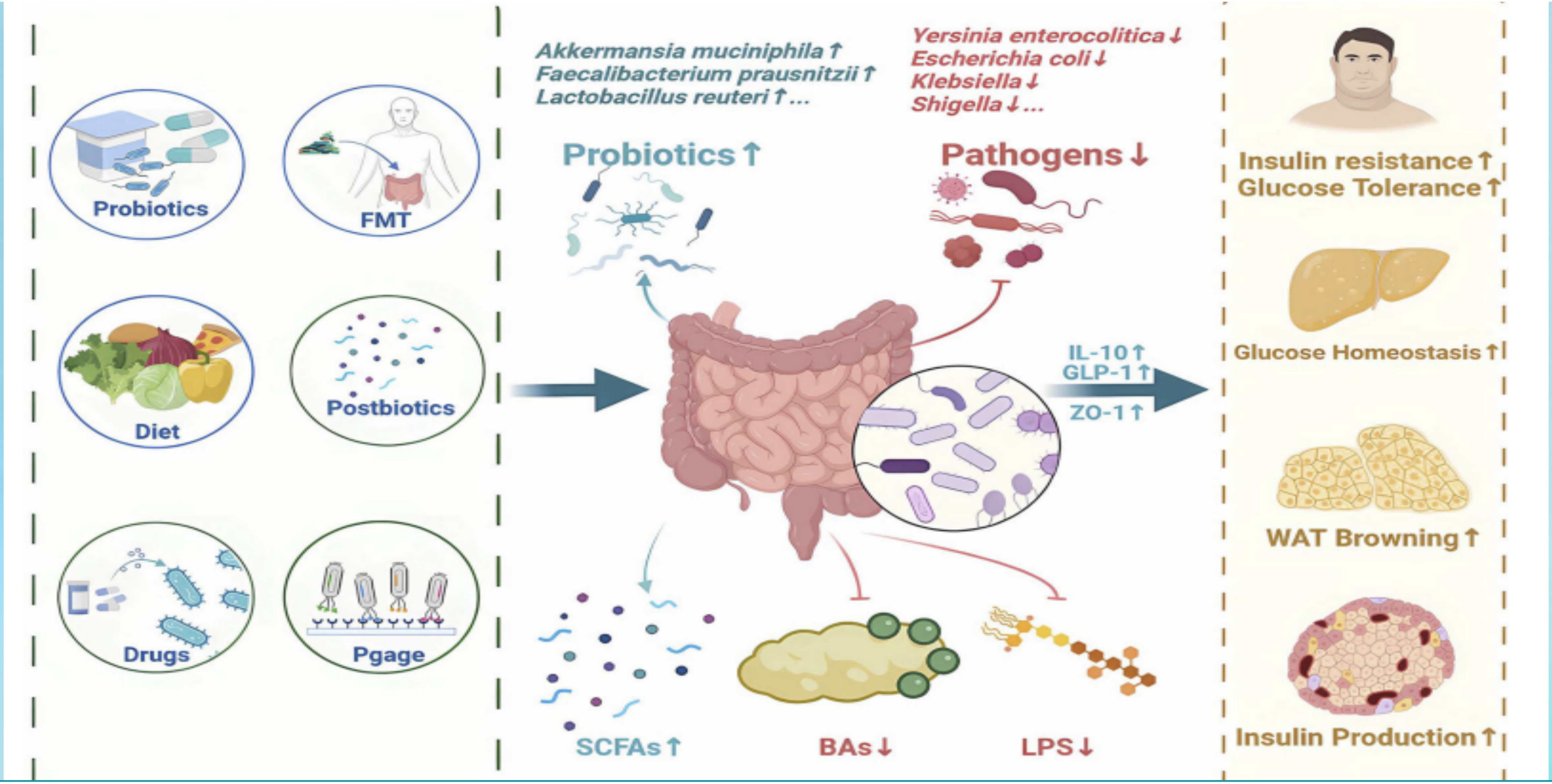
## Prebiotics

- The concept of prebiotic was introduced by Gibson & Roberfroid, in 1995
- "Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon that can improve host health."



| Prebiotics | Probiotics |
|---|---|
| Prebiotics are defined as nonliving non-digestible special form of fiber or carbohydrates. | Probiotics are referred to as live active microorganisms that when administered in adequate amount will have beneficial effects to its host. |
| The powder form of prebiotics can survive heat, cold, acid. | • more fragile.<br>• vulnerable to heat.<br>• may be killed over time. |
| Prebiotics perform their role by nourishing the bacteria that live in the intestines. | Probiotics fight the harmful bacterial species present in the gut. |

# Potential therapy and treatments for T2DM by regulating gut microbiota and its metabolites



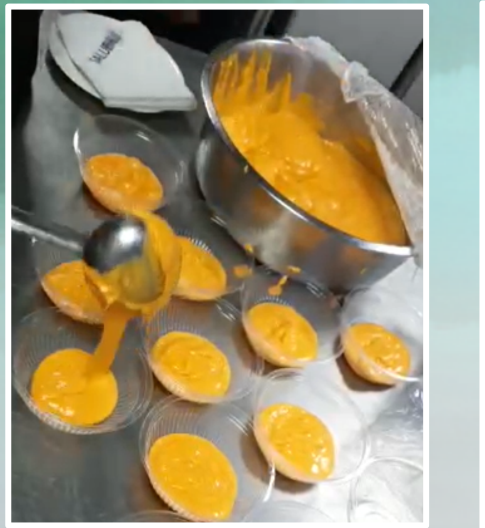
Wu J, Yang K, Fan H, Wei M and Xiong Q (2023) Targeting the gut microbiota and its metabolites for type 2 diabetes mellitus. Front. Endocrinol. 14:1114424. doi: 10.3389/fendo.2023.1114424

# Development of the INDMED diet

## Switching to Steamed and Grilled methods of cooking

## Accurate measurement of each serving

## Switching to Almond milk for MED-ified desserts

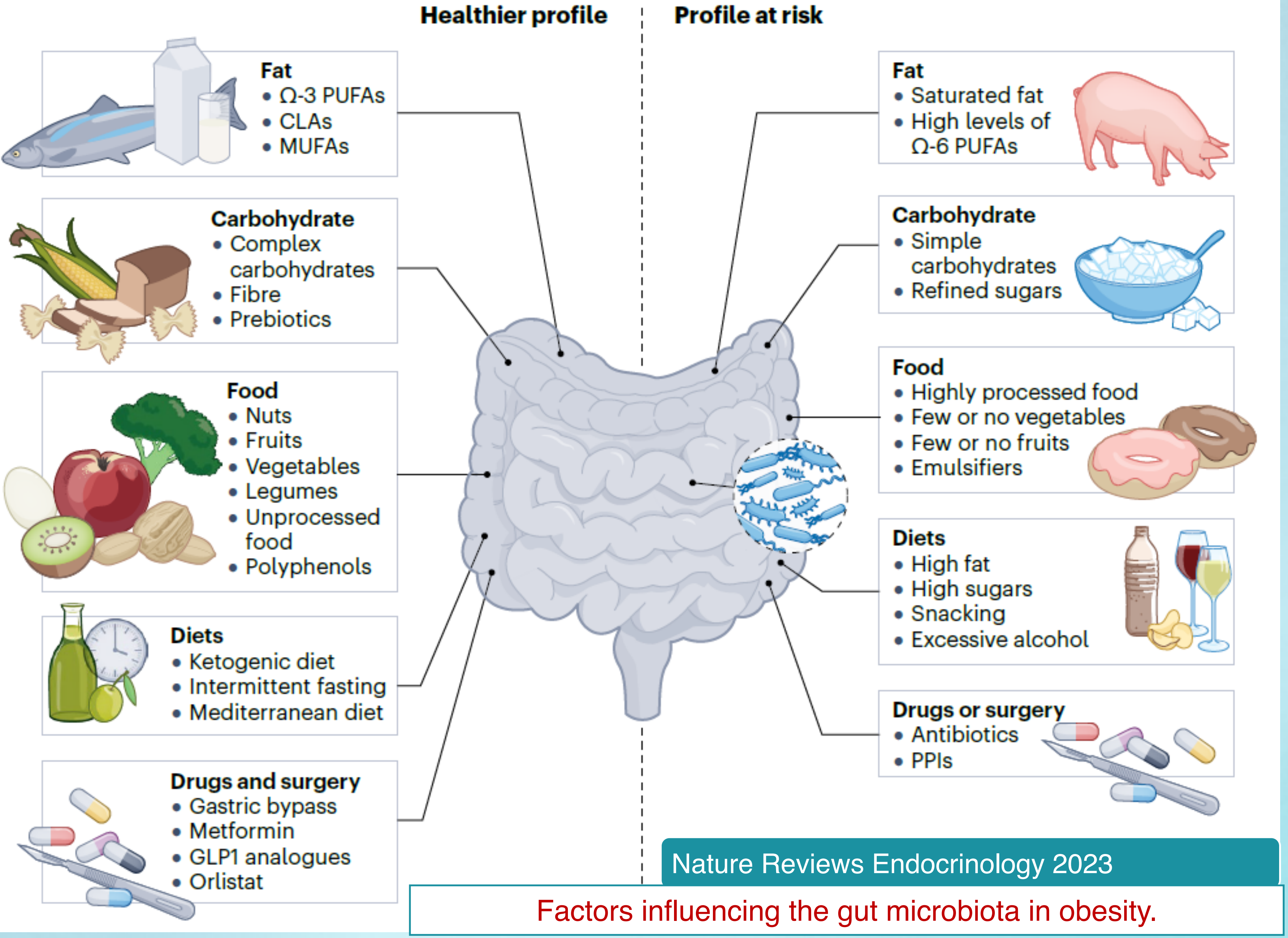


## Switching to whole grains like millets and brown rice

## Use of Extra Virgin olive oil for dressing

## MED-ified Dosa

# The gut microbiota in obesity and weight management:microbes as friends or foe?



**Healthier profile**

**Fat**
- Ω-3 PUFAs
- CLAs
- MUFAs

**Carbohydrate**
- Complex carbohydrates
- Fibre
- Prebiotics

**Food**
- Nuts
- Fruits
- Vegetables
- Legumes
- Unprocessed food
- Polyphenols

**Diets**
- Ketogenic diet
- Intermittent fasting
- Mediterranean diet

**Drugs and surgery**
- Gastric bypass
- Metformin
- GLP1 analogues
- Orlistat

**Profile at risk**

**Fat**
- Saturated fat
- High levels of Ω-6 PUFAs

**Carbohydrate**
- Simple carbohydrates
- Refined sugars

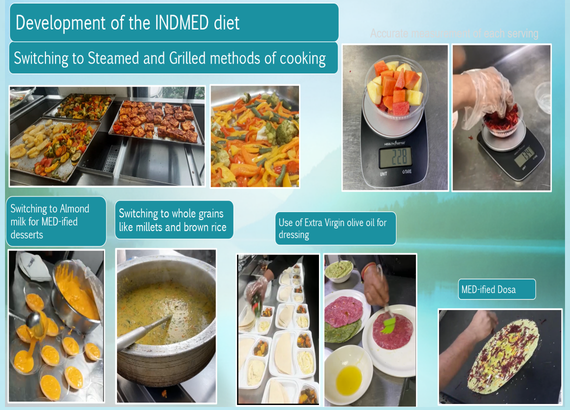
**Food**
- Highly processed food
- Few or no vegetables
- Few or no fruits
- Emulsifiers

**Diets**
- High fat
- High sugars
- Snacking
- Excessive alcohol

**Drugs or surgery**
- Antibiotics
- PPIs

Nature Reviews Endocrinology 2023

Factors influencing the gut microbiota in obesity.



Development of the INDMED diet

Switching to Steamed and Grilled methods of cooking

Accurate measurement of each serving

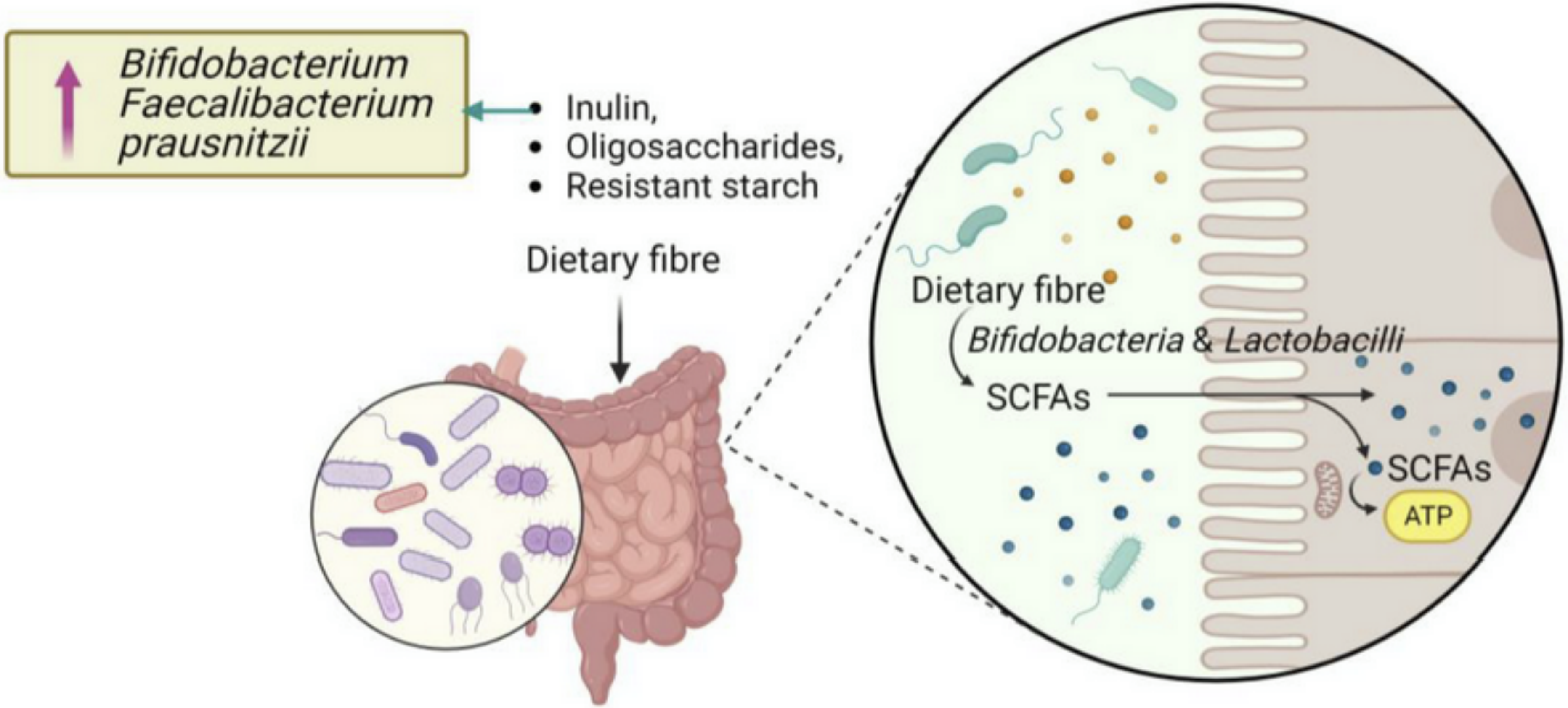
Switching to Almond milk for MED-ified desserts

Switching to whole grains like millets and brown rice

Use of Extra Virgin olive oil for dressing

MED-ified Dosa

Van Hul M, Cani PDNat Rev Endocrinol. 2023 May;19(5):258-271. doi: 10.1038/s41574-022-00794-0. Epub 2023 Jan 17. PMID: 36650295.



↑ *Bifidobacterium*
*Faecalibacterium prausnitzii*

- Inulin,
- Oligosaccharides,
- Resistant starch

Dietary fibre

**Sulfur-containing compounds**

- Garlic
- Onions
- Cruciferous vegetables : broccoli, cauliflower & kale

**Alkaloids**

- Caffeine
- Beans
- Theanine
- Codeine

**Essential oils**

- Oregano
- Thyme
- Lavender
- Citrus peel
- Echinacea
- Ginseng

**Flavonoids**

- Citrus fruits
- Soybeans
- Parsley
- Ginkgo biloba

**Anthocyanins**

- Cranberries
- Raspberries
- Strawberry
- Red grapes

**Carotenoids**

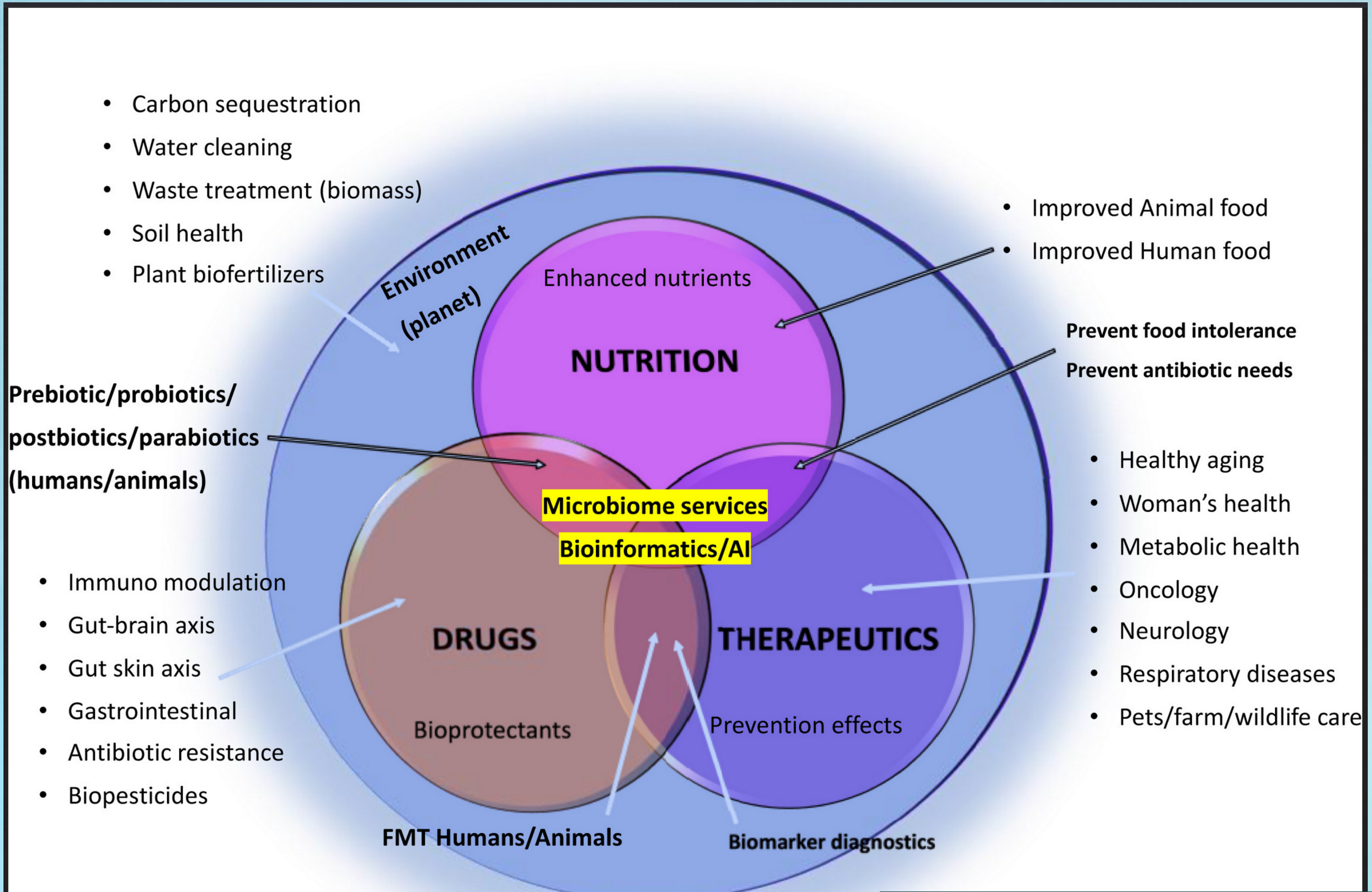
- Fruits
- Vegetables: tomatoes, carrots & spinach

**Polyphenols**

- Green tea
- Berries
- Cocoa
- Apple
- Onions
- Curcumin

Benameur, T.; Porro, C.; Twfieg, M.-E.; Benameur, N.; Panaro, M.A.; Filannino, F.M.; Hasan, A. Emerging Paradigms in Inflammatory Disease Management: Exploring Bioactive Compounds and the Gut Microbiota. Brain Sci. 2023, 13, 1226. https://doi.org/10.3390/brainsci13081226

# Vision 2050



- Carbon sequestration
- Water cleaning
- Waste treatment (biomass)
- Soil health
- Plant biofertilizers

**Environment (planet)**

- Improved Animal food
- Improved Human food

Enhanced nutrients

**NUTRITION**

**Prevent food intolerance**

**Prevent antibiotic needs**

**Prebiotic/probiotics/**
**postbiotics/parabiotics**
**(humans/animals)**

**Microbiome services**

**Bioinformatics/AI**

- Healthy aging
- Woman’s health
- Metabolic health
- Oncology
- Neurology
- Respiratory diseases
- Pets/farm/wildlife care

- Immuno modulation
- Gut-brain axis
- Gut skin axis
- Gastrointestinal
- Antibiotic resistance
- Biopesticides

**DRUGS**

Bioprotectants

**THERAPEUTICS**

Prevention effects

**FMT Humans/Animals**

**Biomarker diagnostics**

https://doi.org/10.1016/j.soh.2024.100065

Holistic view of health solutions microbiome centric. Nutrition, Drugs and Therapeutics are related to human-animals, embedded into a living environmental system.

# Take Home Points

- Over the past two decades, alterations in the GM have been associated with aberrant glucose metabolism and steatosis in individuals with diabetes.

- Larger sample sizes in epidemiological studies have now started to show the magnitude and possible consistency of correlations between the GM and human metabolic traits of relevance to obesity and/ or type 2 diabetes; however, for type 1 diabetes, the picture is much less clear.

- Interaction with diabetes medications in relation to ethnicity and dietary intake should be taken into account more rigorously in future studies.

- Moreover, in recent years, more insights have been gained into the function of the GM beyond just its composition, and this information nicely dovetails with earlier reports of links between specific metabolites, including SCFAs, BCAAs and bile acids, and obesity and diabetes.

- With regard to GM composition, only a few studies have addressed the role of phages and fungi and the interactions between these inhabitants and bacterial strains in diabetes.

- It is clear that future studies also need to focus on small intestine microbiota function, as well as developing adequate bioinformatic pipelines and correctly assembling genomes .

- We must also take into account that most data to date have been generated in mouse studies, whose relevance to human diabetes needs further confirmation because of the large differences between mice and humans in diet, genetics, and life span.

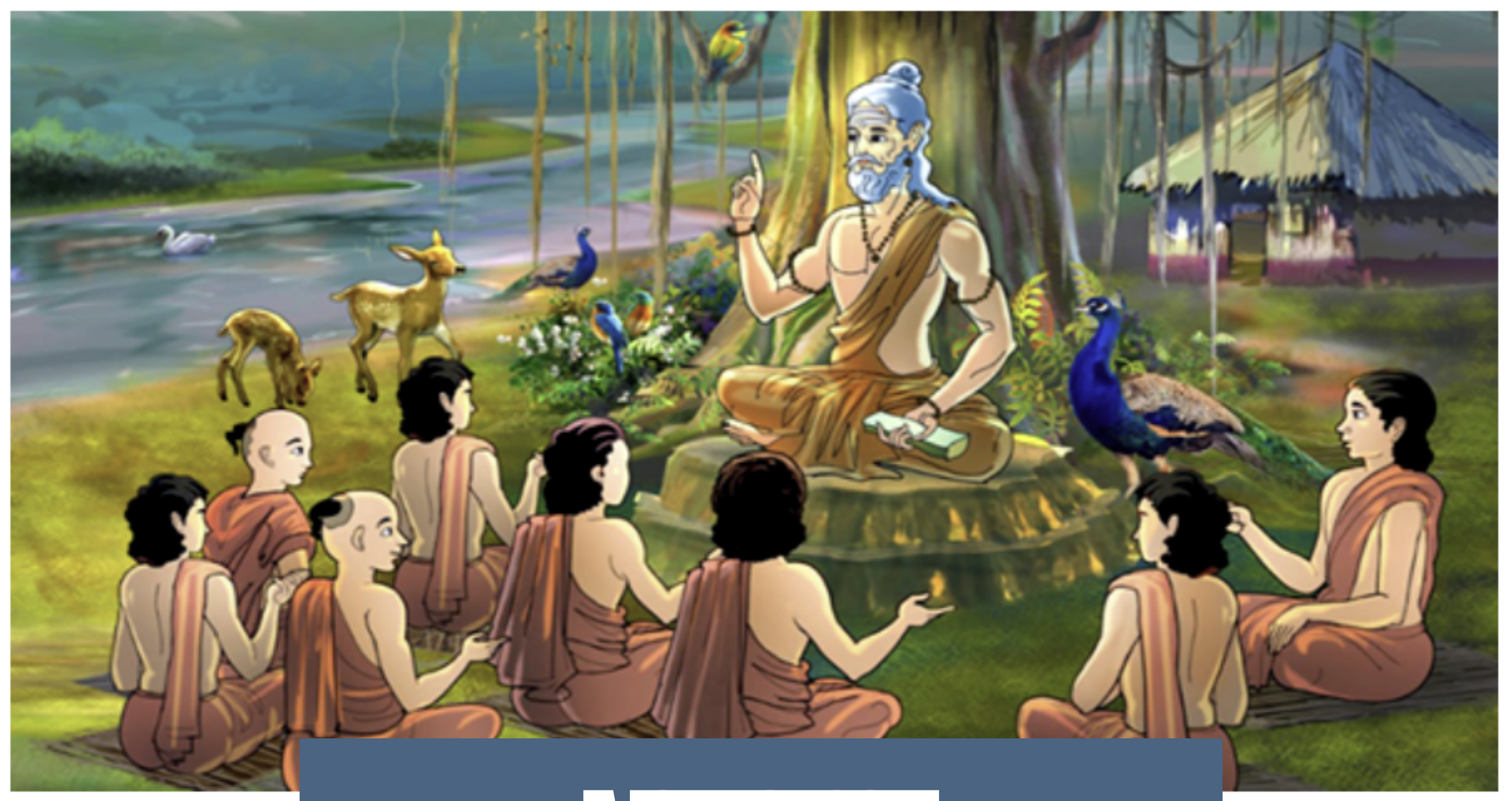
- Nevertheless, human intervention studies of single strains and FMT in the setting of human diabetes have shown a range of clinical metabolic effects (compared with the more consistent effects of medications), yet without serious side effects.

# We need to learn more before advocating for microbial-based disease interventions.

The understanding of the microbiome and its influence on human health is really in its early stages, and, at present, one must be cautious about applying interventions such as probiotics, which claim to influence disease and outcomes.

Finally, it is vital to recognize the human as a whole and understand that manipulations of any factor in one direction can have implications in another.

# अनुगृहीतोऽस्मि



**धन्यवाद**

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