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PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA
وزارة التعليم العالي والبحث العلمي
MINSTRY OF HIGH EDUCATION AND SCIENTIFIC RESEARCH

Fréres Mentouri Constantine1 University
Faculty of Natural Sciences and Life

جامعة الاخوة منتوري قسنطينة1
كلية علوم الطبيعة والحياة

قسم الكيمياء الحيوية/ البيولوجيا الخلوية والجزيئية
Department of Biochemistry/ Molecular and Cellular Biology

Dissertation

To Get Diploma of Master in Biochemistry

Sector: Biological Sciences

Option: Biochemistry

Entitled:

Effect of Diet on Gut Microbiota

Done by:

LEHOUT Maroua

ASBILE Roufeida

Date of submission: July 14th, 2021

Examination Board:

President: Y. NECIB (Pr. at Frères Mentouri Constantine 1 university)

Supervisor: A. KHEDARA (Dr. at Frères Mentouri Constantine 1 university)

Examiner: S. MOUSSAOUI (Dr. at Frères Mentouri Constantine 1 university)

Academic year
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LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ARP: Appetite-regulating peptides.

C. histolyticum: *Clostridium histolyticum.*

C. perfringens: *Clostridium perfringens.*

CD: Crohn's disease**.**

Clostridium spp.: Clostridium species.

CMC: Carboxyl methyl cellulose.

CMC: Carboxymethyl cellulose.

CRC: Colorectal cancer**.**

CRF: Corticotrophin releasing factor.

CRP: C-reactive protein.

C-section, CS: Cesarean section.

CVD: Cardiovascular disease.

DF: Dietary fiber**.**

DM: Diabetes mellitus**.**

E. rectale*: Eubacterium rectale.*

F. prausnizzi: *Faecalibacterium prausnitzii.*

GABA: G-Aminobutyric acid.

GI: Gastrointestinal.

GIT: The gastrointestinal tract.

GM: Gut microbiota.

GSIS: Glucose- stimulated insulin secretion.

HMP: the Human Microbiome Project.

HPA: The hypothalamic- pituitary-adrenal.

IBD: Inflammatory Bowel Disease.

IGN: Intestinal gluconeogenesis.

IPA: Indole propionic acid.

LDL: Low-density lipoprotein.

LPS: Lipopolysaccharide.

LPS: Lipopolysaccharide.

MACs: Microbiota-accessible carbohydrates .

MDPs: Mediterranean dietary patterns.

MedDiet, MD: Mediterranean diet.

MetaHIT: METAgenomics of the Human Intestinal Tract.

MUFAs: Monounsaturated fatty acids.

NAS: Non-caloric artificial sweetener.

NASs: Non-caloric artificial sweeteners.

NIH: The National Institute of Health.

NNS: Non-nutritive sweeteners.

OUT: Operational Taxonomic Unit.

P80: Polysorbate-80.

PAMPs: Pathogen- associated molecular patterns.

Pp: Postpartum.

PSA: Polysaccharide A.

PUFAs: Polyunsaturated fatty acids.

RA: Rheumatoid arthritis.

SCFAs: Short chain fatty acids.

SFAs: Saturated fatty acids.

T1D: Type 1 diabetes.

T2D: Type 2 diabetes.

TMAO: Trimethylamine *N*- oxide.

TMAO: Trimethylamine N-oxide.

TMAO: Trimethylamine oxide.

Treg cells: T regulatory cells.

UC: Ulcerative colitis.

UCP1: Uncoupling protein 1.

Ufa: Unsaturated fatty acids.

VD: Vaginally delivered infants.

WD: Western one.

TABLE OF CONTENTS

Chapter three: Impact of food altering gut microbiota

Introduction

Introduction

Over a century ago, the existence of dense populations of microorganisms in animal and human digestive tracts have been established, a microbial community which has co-evolved with the host to form a mutually beneficial relationship **(Ishiguro et al., 2018)**. However, this relationship has significantly affected the collective human microbiome as a result of changes in the environment, social norms and especially dietary habits. These disruptions in the intestinal host-microbe interactions can result in miscues and altered host responses, increasing the risk of pathogenic processes **(Sun et al., 2014).** To deal with the subject, the following question will be answered through the present study: how diet influences the gut microbiota and how does it affect our health?

The purpose of this work is to explain what the gut microbiota is, the many functions it serves, how can it be either harmed or supported by what we eat, and the role it may play in various diseases and in determining our overall health. The approach being used to carry on this work is descriptive analysis study where different theoretical aspects have been highlighted.

Chapters 1 is going to cover general concepts about the gut microbiome, its composition and functionality, age-related changes throughout life from infancy to older adulthood, and explains the environmental factors that appear to influence the gut microbiota, setting the basis for the following chapters, Chapter 2 looks into nutrition and discusses how various food components affects microbiota composition and function in humans considering which diets may disrupt the normal microbiota, and Chapter 3 describes how the gut microbiota is related with different states of health and diseases and shows how the gut microbiota can be controlled through interventions in disease.

Chapter one:

Human gut microbiota

Chapter one: Human gut microbiota

For the past decade, human gut microbiota has been extensively studied as more and more scientists believe that human health, apart from our own genome, largely depends on microbes that are living on/in our body **(Zhu et al, 2010).**

1. Human microbiota

According to the Oxford English Dictionary, the definition of microbiota is "microfauna and microflora considered together; specifically that of a given habitat, region or epoch." In humans, microbiota is "the microbial taxa associated with humans" **(Liu, 2021).**

Our microbial community, known as the human microbiota, is made up of bacteria, yeasts, and other Eukarya, archaea (primitive single-cell organisms), fungi, protozoa and non-living viruses (bacteriophages), that resides in and on different body niches such as mammary glands, placenta, oral cavity, urogenital tract, respiratory tract, skin, and gastrointestinal tract **(Fig. 1)**. In addition, the human microbiota has been shown to be associated with a variety of conditions including gastric ulcers, eczema, dental cavities, and even cancer **(Marchesi and Ravel, 2015; Althani, 2016; Liu, 2016).**

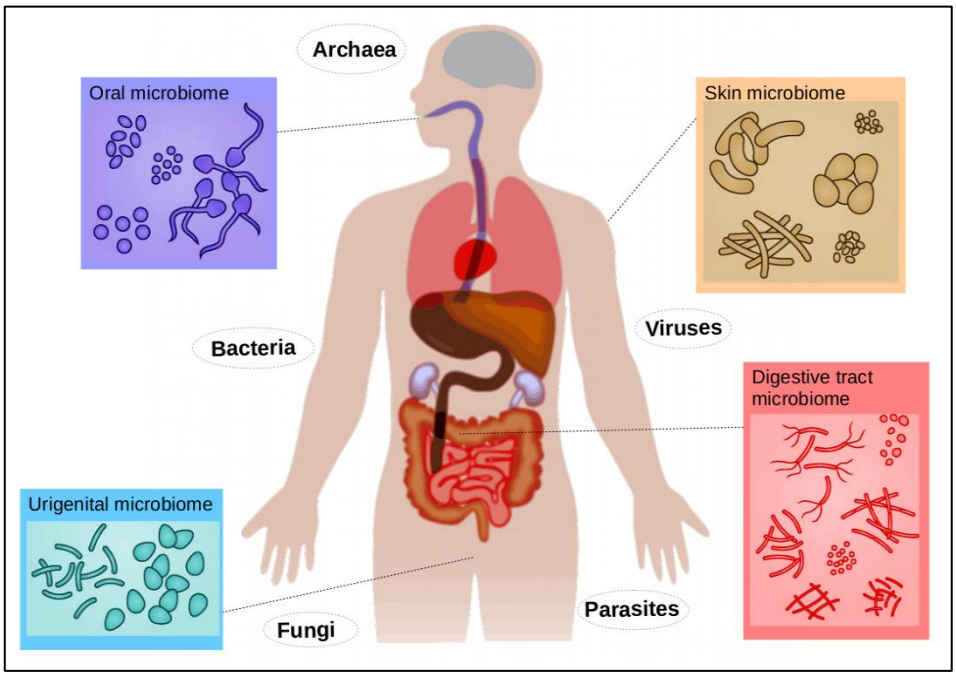


Fig. 1 Human Microbiome (net 01).

In our body, the microbiome has essential functions in the body such as development of immunity, defense against pathogens, host nutrition. Furthermore, this latter function, in turn, includes production of short-chain fatty acids, synthesis of vitamins and fat storage as well as an influence on human behavior, making it an essential organ of the body without which we would not function correctly **(Fig. 2) (Amon and Sanderson, 2017)**.

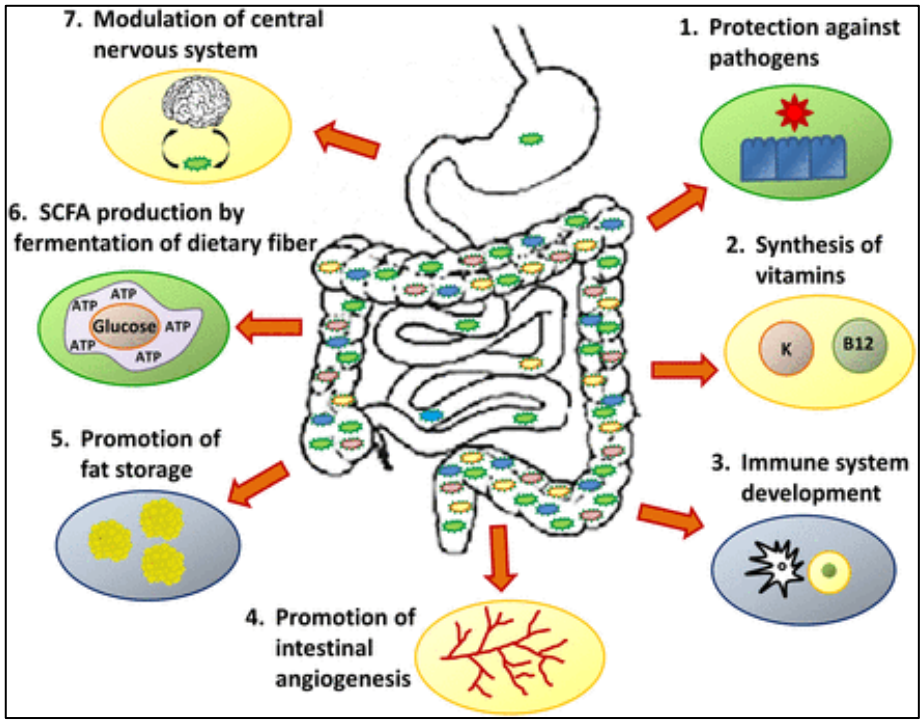
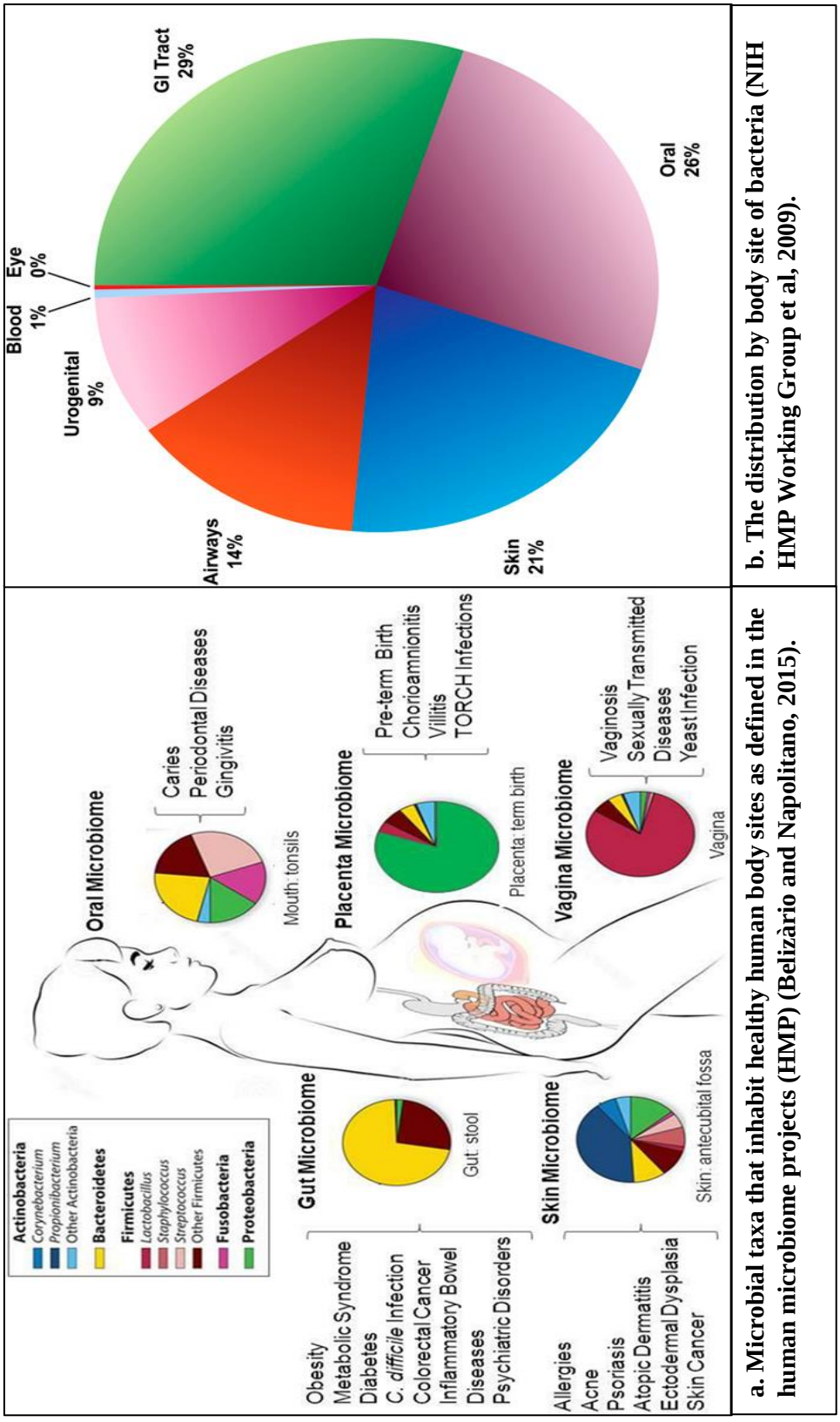


Fig. 2 The human microbiome functions (Amon and Sanderson, 2017).

1. 1. Human microbiome project

In 2008, the National Institute of Health (NIH) initiated the Human Microbiome Project (HMP) in an effort to gain a more complete and thorough understanding of human microbiomes at different body locations and their associations with diseases (**Liu, 2016).** The HMP Consortium has reported the structure and function of the human microbiome in 300 healthy adults (18–40 years old) at 18 body sites from a single time point. This has led to an unprecedented amount of data about the complexity of the human microbiome, allowing for a baseline for further research into the impacts of the microbiome on health and disease **(Cresci and Bawden, 2015).**

The first release of the HMP database included microbiome data of nasal passages, the oral cavity, skin, gastrointestinal tract, and urogenital tract **(Belizàrio and Napolitano, 2015)**. **Fig. 3** schematically summarizes the data of these studies.



a. Microbial taxa that inhabit healthy human body sites as defined in the human microbiome projects (HMP) (Belizàrio and Napolitano, 2015).

b. The distribution by body site of bacteria (NIH HMP Working Group et al, 2009).

Fig. 3 The distribution of human microbiome based on HMP results.

2. Definition of gut microbiota

Molecular researcher Joshua Lederberg defines the gut microbiota as "the sum of bacteria and their collective genetic material present in the gastrointestinal tract" (GIT) **(Cresci and Izzo, 2019)**, while **(Young, 2017)** adds that the gut microbiome include not just microbes but also host factors such as the host epithelium, immunological components, and microbe and host products such as metabolites.

The gut microbiota is made up of all bacteria, both commensal and pathogenic, which live in the GIT in a complex state of dynamic equilibrium, that is made up of reciprocal interactions and various networks with the host cells. This is a spatial and temporal equilibrium, whose disruption could lead to dysbiosis **(Parisi et al., 2021).** The total number of microorganisms is predicted to be greater than 10^{14}, which encompasses ≃10 times more bacterial cells than the number of human cells and over 100 times the amount of genomic content (microbiome) as the human genome **(Fig. 4) (Thursby and Juge, 2017).**

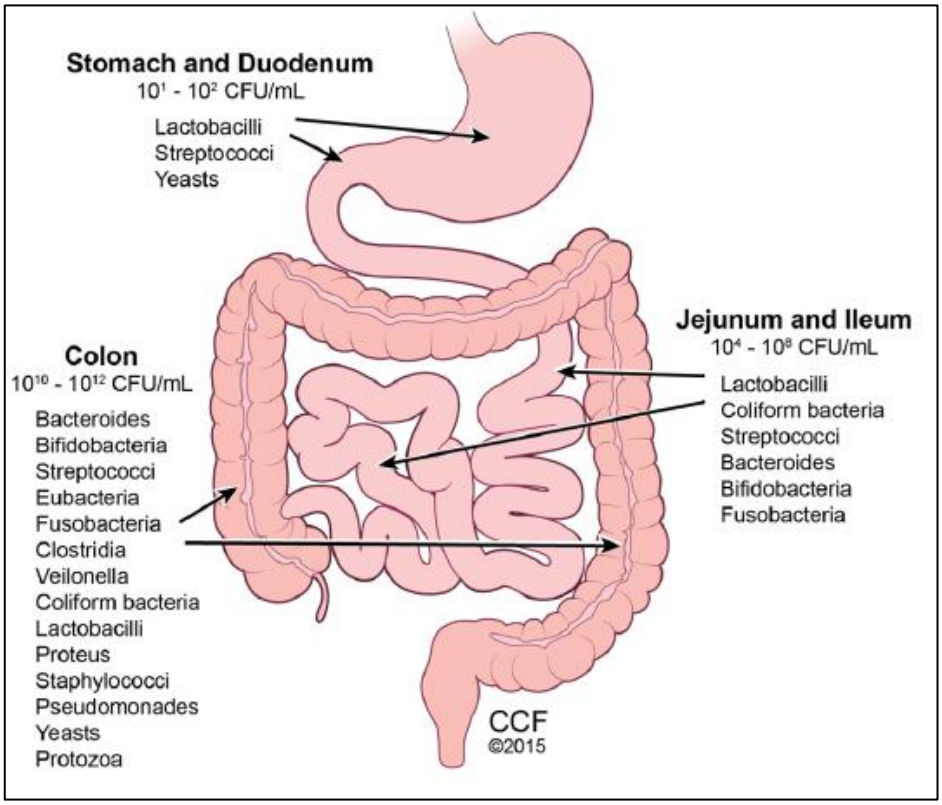


Fig. 4 The human Gut Microbiota (Cresci and Bawden, 2015).

2. 1. Interaction between oral and intestinal microbiota

The gastro-intestinal system includes everything starting from the oral cavity to the rectum and is essentially a continuous pipeline connecting the external environment to the internal. The oral cavity is important for the initiation of digestion and conducts initial immune responses, it includes distinct, small microbial habitats, such as teeth, buccal mucosa, soft and hard palate, and tongue, which form a species-rich heterogeneous ecological system **(Kilian, 2018; Barlett et al, 2020).** A large variety of oral species can reach and colonize the intestinal microbiota directly (Through the esophagus) or indirectly (By the blood cycling route), where they can contribute to the development of both inflammatory colitis and cancerous pathology **(Fig. 5)**. However, constituents of the oral microbiota are not always found in the gut **(Lu et al, 2019; Moutsopoulos and Konkel, 2020).**

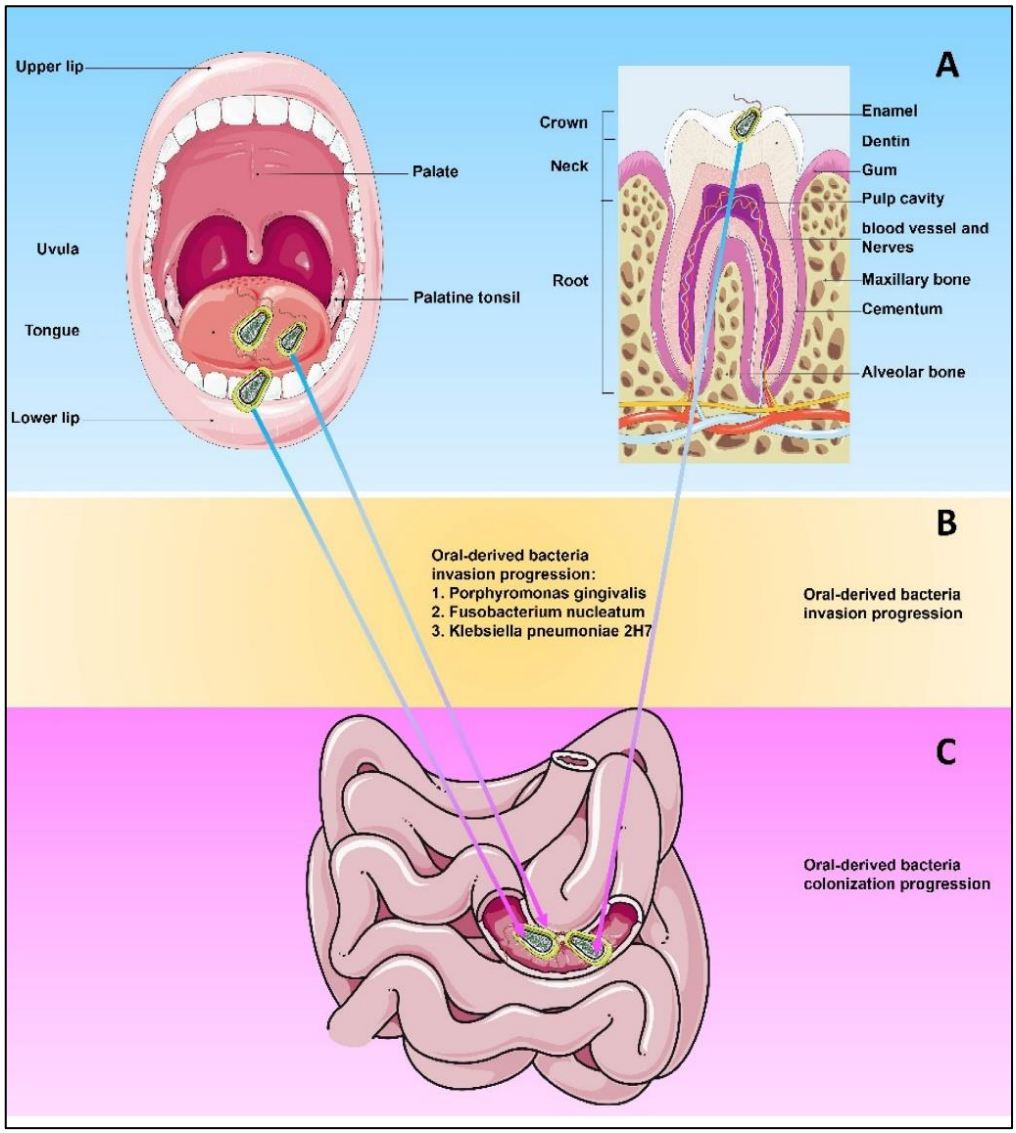


Fig. 5 Oral microbiota can invade gut microbiota directly and indirectly. (A). Basic structure of the oral cavity. (B). Progression of oral-derived bacterial invasion. (C). Progression of oral-derived bacterial colonization **(Lu et al, 2019).**

3. Characteristics

3 .1. Gut microbiota composition

The Gut microbiota is composed of various species of microorganisms, which includes bacteria, yeast, and viruses. Bacteria are categorized into phyla, groups, orders, families, genera, and species according to their taxonomic classification **(Table. 1)**. However, just a few phyla are represented with more than 160 species **(Laterza et al., 2016).**

Table 1. Taxonomy of Escherichia coli as an example (Laterza et al., 2016).

Cellular organisms classification	Example
Kingdom	Bacteria
Phylum	Proteobacteria
Class	Gammaproteobacteria
Order	*Enterobacteriales*
Family	*Enteriobacteriaceae*
Genus	*Escherichia*
Species	*Escherichia coli*

Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia are the dominant gut microbial phyla, with the two phyla Firmicutes and Bacteroidetes that represent 90% of gut microbiota. More than 200 genera make up the Firmicutes phylum, including Lactobacillus, Bacillus, Ruminicoccus, Enterococcus, and Clostridium genera which account for 95% of the Firmicutes phylum. Bacteroidetes is composed of predominant genera such as Bacteroides and Prevotella. The Actinobacteria phylum has a smaller proportion of bacteria and is dominated by the Bifidobacterium genus **(Fig. 6) (Rinninella et al., 2018)**.

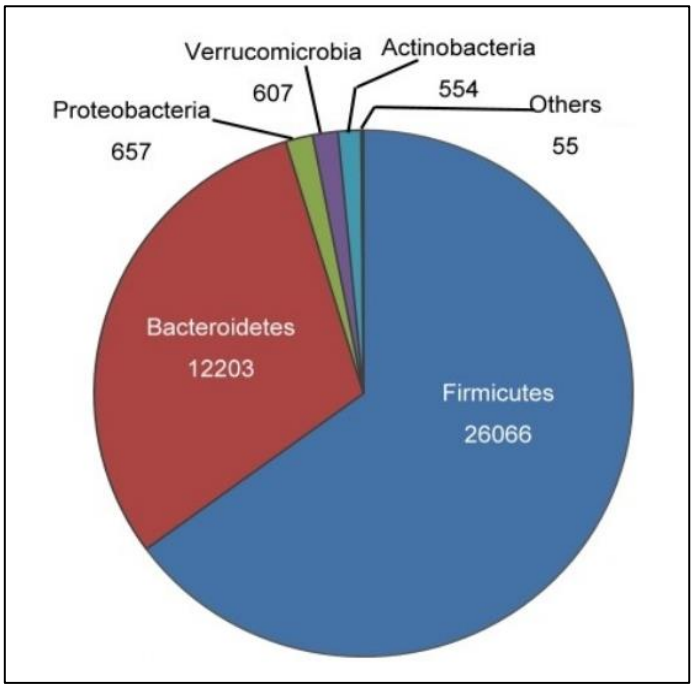


Fig. 6 The distribution of bacterial species isolated from the gut according to the phylum to which they belong (Net 02).

There is a marked difference in diversity and number of bacteria from the esophagus distally to the rectum, ranging from 10^1 per gram of contents in the esophagus and stomach to 10^{12} per gram of contents in the colon and distal gut **(O'Hara and Shanahan, 2006).**

Streptococcus presents the dominant genus in the distal esophagus, duodenum and jejunum. Besides, the dominant genera in the stomach and which defines the gastric flora's entire microbial landscape is Helicobacter **(Jandhyala et al., 2015).**

The composition and the abundance of the intestinal microbiota in the entire gastrointestinal tract are different. The gastrointestinal tract is a system that is divided into many different anatomical areas from the stomach to the rectum, each of these anatomical parts has its own set of physicochemical characteristics, such as local pH, redox potential, transit rates of the luminal content, availability of diet-derived compounds, and host secretions (e.g., hydrochloric acid, digestive enzymes, bile, and mucus) **(Kovatcheva-Datchary et al., 2013).** The density and composition of the gut microbiota are affected by immunological gradients and host genetics along the gut and by some environmental factors, such as diet **(Fig. 2) (Li et al., 2014; Thursby and Juge, 2017).**

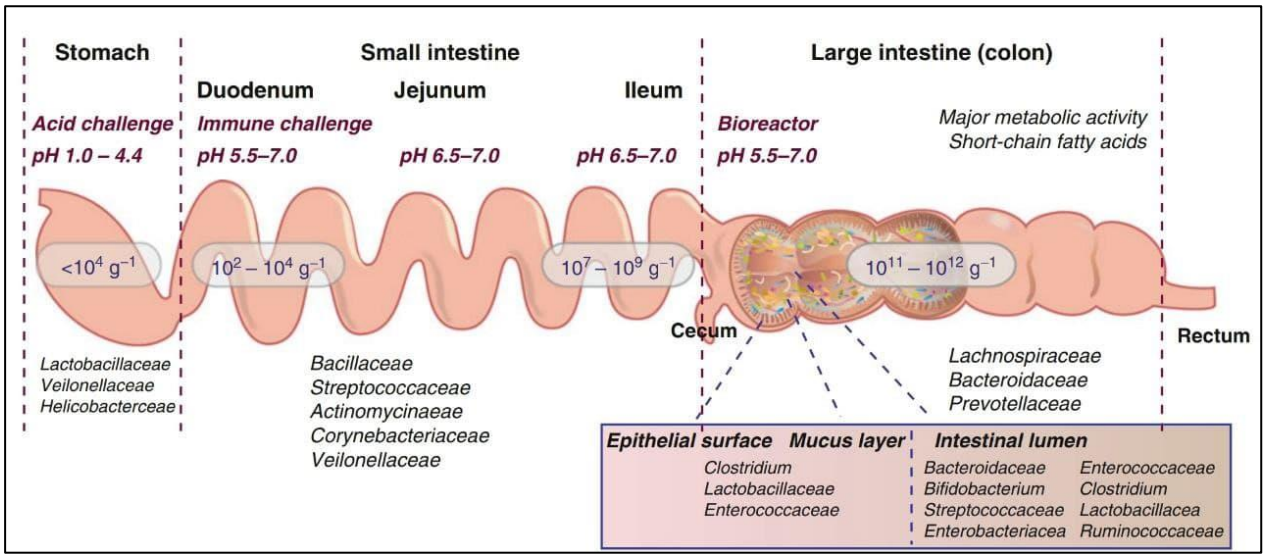


Fig. 7. Gut microbiota composition and number variations along the GI tract. Major features that shapes the gut microbiotas into different anatomical regions of the gut are indicated (Kovatcheva-Datchary et al., 2013).

Along the gut, the microbiota composition differs from region to another. Where the microorganisms in the mucus and epithelial crypts are significantly different from that found in luminal content and feces. As an example to that Bacteroidetes, which tend to be more abundant in faecal/luminal samples than in the mucosa and Firmicutes, specifically *Clostridium cluster XIVa*, which are more abundant in the mucus layer than in the lumen **(Kovatcheva-Datchary et al., 2013; Thursby and Juge, 2017).**

Although, Microbiotas of various compositions may share some functional redundancy, resulting in protein or metabolite profiles that are identical **(Moya and Ferrer, 2016).** This information is essential for the advancement of therapeutic techniques to alter and shape the microbial environment in disease **(Thursby and Juge, 2017).**

Besides the healthy gut microbiota, which is predominantly constituted by the phyla Firmicutes and Bacteroidetes, primary pathogens can also be found in the human colon with a low abundance (0.1% or less of entire gut microbiome), for example species such as *Campylobacter jejuni*, *Salmonella enterica*, *Vibrio cholera*, *Escherichia coli (E. coli)*, and *Bacteroides fragilis* **(Jandhyala et al., 2015).**

The MetaHIT Consortium (Metagenomics of the human intestinal Tract consortium – a project to understand the role of the human intestinal microbiota in health and disease-) has proposed another way of classifying the gut flora based on species composition which clusters into well-balanced host-microbial symbiotic states that remain constant over geography and gender, however, diet and drugs may have a different effect on them. These clusters have been named Enterotypes. Traditionally, three enterotypes of bacterial patterns have been identified, Enterotype 1 (high Bacteroides abundance), Enterotype 2 (high Prevotella abundance), and Enterotype 3 (high Ruminococcus abundance) **(Fig. 8)**. The Prevotella enterotype was closely linked to a carbohydrate-rich diet, while the Bacteroides enterotype was linked to a protein and animal-fat-rich diet, such as the Western diet **(Hollister et al., 2014; Moraes et al., 2019).**

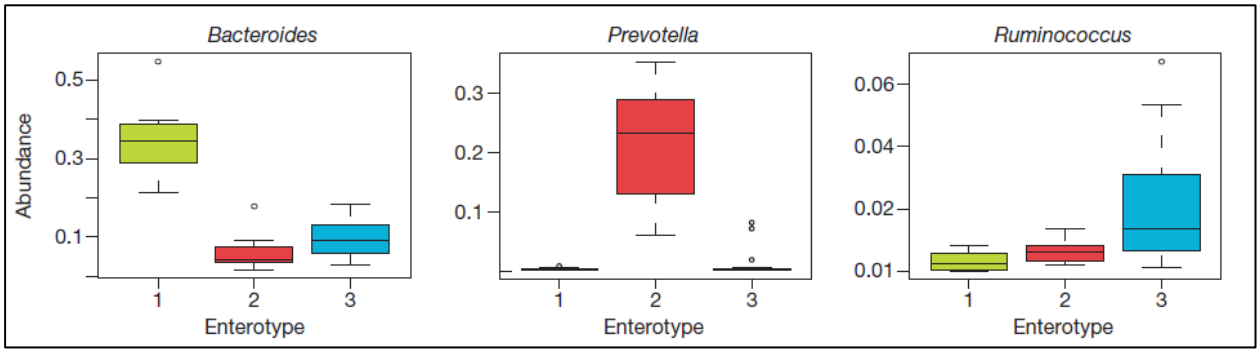


Fig. 8 Enterotypes differences and abundances of the main contributors of each enterotype (Arumugam, 2011).

3. 2. Gut microbiota dynamic

3. 2. 1. Colonization of the intestinal microbiota during early life

The infant gut is thought to be sterile until it is colonized by microorganisms residing in the environment at birth**.** However, recent studies have provided indications of bacterial presence in amniotic fluid, fetal membranes, umbilical cords, placentas, and meconium in healthy full-term pregnancies. Although, several other studies have put forward arguments against such a possibility of in utero gut colonization **(Voreades, 2014; Tanaka and Nakayama, 2017; Milani et al., 2017; Zhuang et al., 2019)**.

Colonization of the infant gut indicates the formation of a diverse microbial community at birth, a process that is influenced by a variety of environmental and host factors **(Milani et al., 2017).** In different body habitats, human adults have highly diverse bacterial communities, but these communities appear to be mostly undifferentiated in newborn infants **(Costello et al., 2009).**

Mammalian placentas give birth through a microbe-infested birth canal and the vagina provide the primary inoculum for all mammals also as the human vagina which is an ecosystem dominated by relatively few bacterial species that changes during pregnancy, to provide newborns with beneficial microbes **(Fig. 9) (Dominguez-Bello et al., 2011).**

Babies born vaginally get their mother's vaginal microbes at birth. These bacteria are found on the skin and in the mouth, as well as in the first meconium. As a result, the different body sites of newborns are colonized with essentially the same microbiota that was acquired vertically from their mothers, and the diverse microbial communities found at these sites in adults develop only later **(Zhuang et al., 2019).**

Meconium microbiotas are different from the microbiotas found in a pregnant woman's vagina, feces, or skin, but they resemble the microbiota found in amniotic fluid, suggesting that microorganisms in the meconium come from the mother's uterus. The GI tract of a fetus looked to be colonized by bacteria through amniotic fluid that was swallowed. Furthermore, the type of microbiota found in the meconium was linked to maternal variables such as allergy history, which could have implications for children's health **(Tanaka and Nakayama, 2017).**

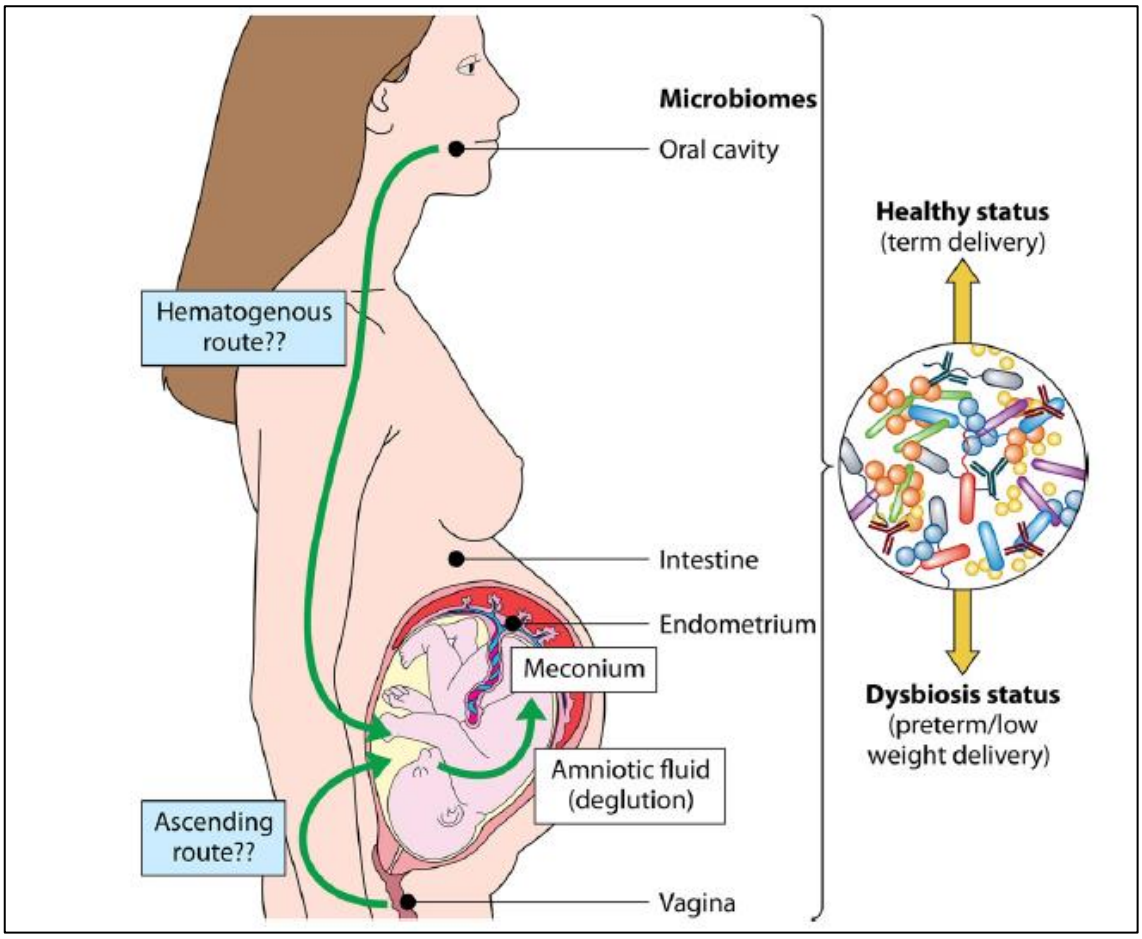


Fig. 9 The maternal microbiome and the associated routes that result in vertical microbial transmission to the newborn are represented in the mother's portrayal (Milani et al., 2017).

3. 2. 2. Development of the intestinal microbiota after birth

The bacteria that live in our gastrointestinal system form a dynamic community that evolves throughout the lifespan of an individual. Because of the quick and dramatic fluctuations observed, the early years of infancy and childhood are characterized by a microbiological condition that has been described as chaotic. At a young age, the microbiota of tiny children begins to resemble that of adults **(Fig. 10) (Voreades, 2014).**

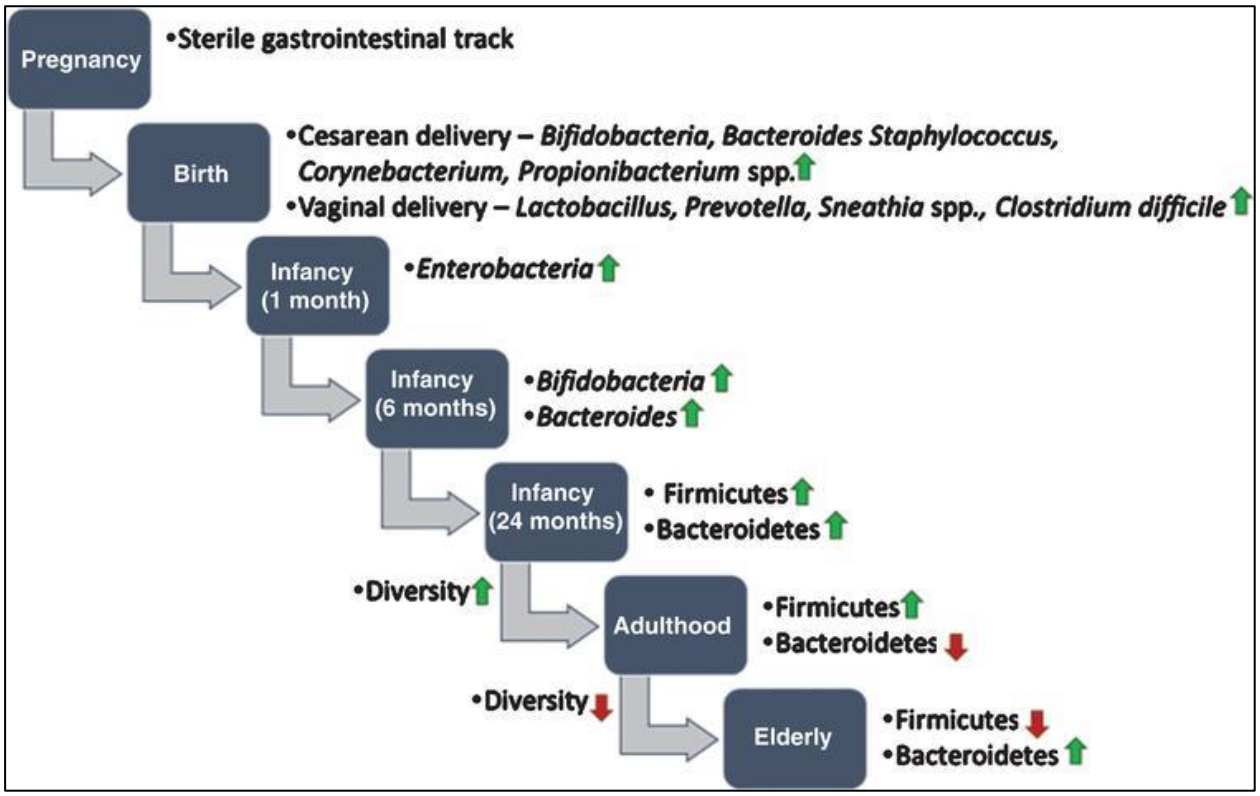


Fig. 10 Development of human gut microbiota from prenatal to elderly (Kumar et la., 2016).

Adults' gastrointestinal microbial communities are commonly thought to be stable, although there is evidence that they change through life at a slower rate than children's **(Dominguez-Bello et al., 2011).** Several factors have been associated to different gut microbiome compositions at discrete time periods and variance in microbial successional trajectories during this critical window of development, including mode of delivery, early-life food, antibiotic use, pet exposure, sex, and mother health **(Durack and Lynch, 2018).**

Microbes colonize the infant during the time of birth as a result the gut microbiota of a baby will be quite similar to the microbiota it encountered at delivery. Infants born vaginally have gut microbiotas that are similar to their mothers' vaginal microbiotas, but infants delivered through caesarean section have microbiotas that are most similar to skin microbiotas **(Zhuang et al., 2019; Tanaka and Nakayama, 2017).**

The infant gut microbiome undergoes a second change at the age of 1–2 years old, and the stable adult microbiome emerges, demonstrating the importance of nutrition in shaping the microbial community **(Voreades, 2014).**

By 3 years of age, the fast proliferation of bacterial diversity observed in the first year of life has slowed significantly, and the composition of the gut microbiome has become more stable by 5 years of age, attributing. Nonetheless, compared to healthy adults, children's gut microbiomes are less diversified and functionally unique **(Durack and Lynch, 2018)**. By preadolescence (7–12 years of age), the complexity of the gut microbiota (number of taxa and functional genes) has often reached adult levels, yet microbial communities at this age are taxonomically and functionally distinct from those of adults **(Hollister et al., 2015).**

Despite the taxonomic diversity and individual nature of the human gut microbiome in adulthood, its functional characteristics are largely similar throughout healthy adult populations **(Durack and Lynch, 2018; Faith et al., 2013).**

Gut microbiomes become more unstable and diverse as people age, a characteristic that has been related to frailty and decreased immunological function. Low gut microbiota richness, which is a proxy for the loss of microbial species and their repertoire of functional genes, appears to be a predictor of mortality in elderly populations, although enrichment of certain bacteria is related to longevity **(Fig. 11) (Odamaki et al., 2016; Ticinesi et al., 2017).**

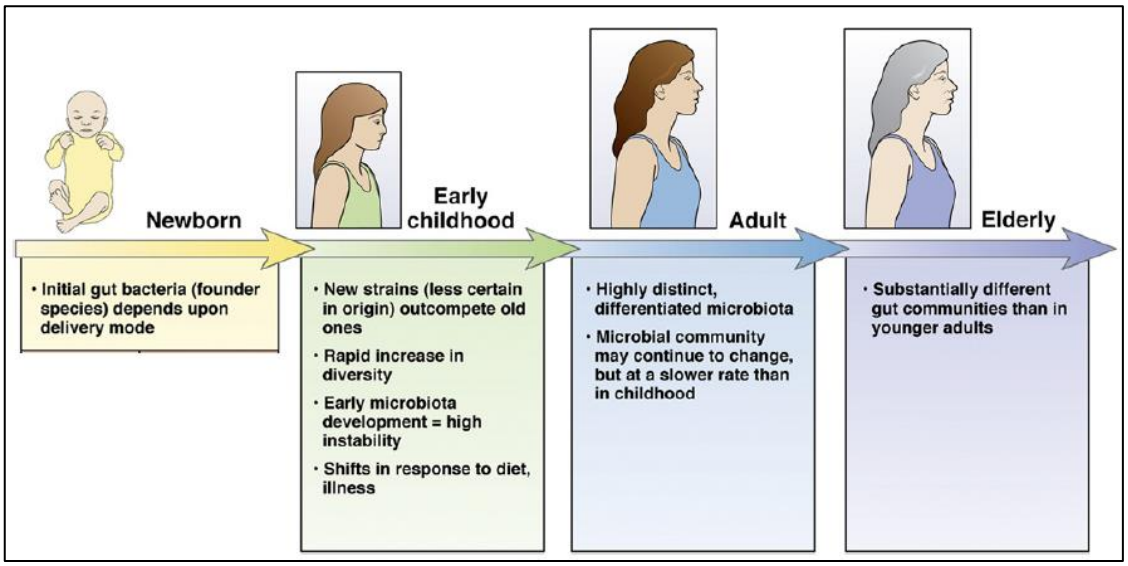


Fig. 11 A diagram depicting the development of the microbiota from the first inoculum as a child to lifelong changes influenced by nutrition, genetics, and the environment (Dominguez-Bello et al., 2011).

Breast milk and formula feeding are two infant feeding methods that have a significant impact on the gut microbiota's development in early life (**Tanaka and Nakayama, 2017).** More than 700 bacteria species have now been found in human colostrum and breast milk, including various lactic acid bacteria species as well as bacteria that commonly colonize newborn's oral cavity, The chemical composition of breast milk does influence the gut microbiome through supplying unique oligosaccharides **(Voreades, 2014).**

It's been widely known that the gut microbiome of formula-fed and breastfed infants differs. Breastfed babies' gut microbiome is less diversified **(Zhuang et al., 2019).** Breastfeeding cessation, rather than solid food introduction, has been reported to be a major microbiota-influencing event. The solid food introduction is associated with a higher bacterial load and diversity **(Derrien et al., 2019).**

In addition to delivery and feeding modes, other factors that influence newborn gut microbiota colonization include gestational age at birth, geographic location, family lifestyle, host genetics, and antibiotic use **(Fig. 12) (Zhuang et al., 2019; Milani et al., 2017)**

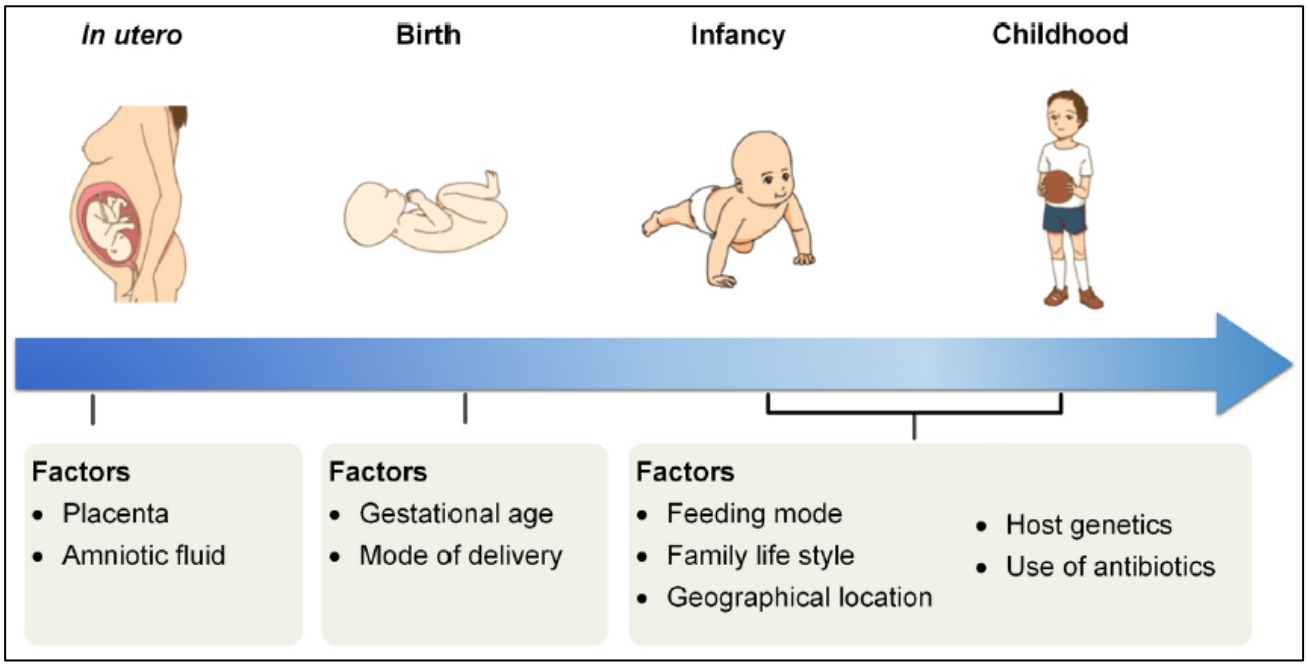


Fig. 12 Factors that shape the intestinal microbiota during early life and development (Zhuang et al., 2019).

3. 3. Gut microbiota functions

The gut microbiota has a number of beneficial properties for the host due to its significant genomic content and metabolic complement, and it performs certain important functions that the human body is incapable of executing, resulting in a symbiotic relationship between microbiota and the human body (**Fig. 13**) **(Thursby and Juge, 2017; Shabana et al., 2018).**

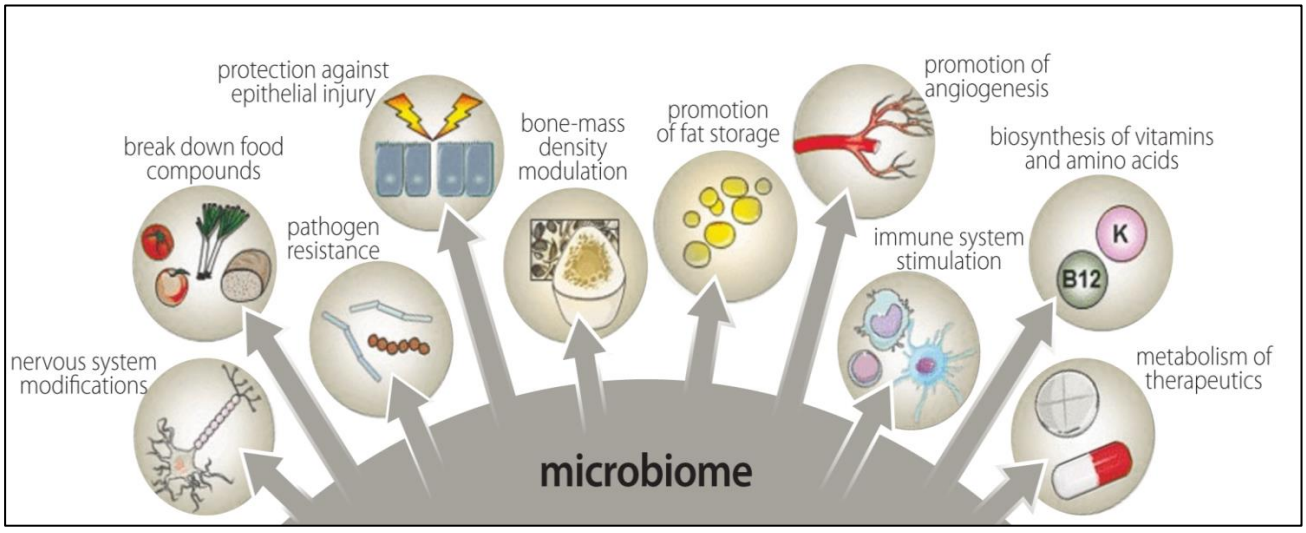


Fig. 13 Functions of gut microbiota (Net 03).

In a healthy person, the intestinal microbiota has also a mutually beneficial relationship with the gut mucosa and performs important metabolic, defensive, and trophic functions **(Fig. 14) (Jandhyala, 2015; Ramirez et al., 2020).** These functions include host nutrition, synthesis of vitamins, fat storage, conversion of cholesterols and bile acids to bile salts, development of the intestinal microvilli, the induction of mucosal tolerance, angiogenesis, detoxification and clearance of toxins and carcinogens, protecting against pathogens**,** as well as an influence on human behavior **(Shabana et al., 2018; Amon and Sanderson, 2017; Kovatcheva-Datchary et al., 2013**; **Laukens et al., 2016).**

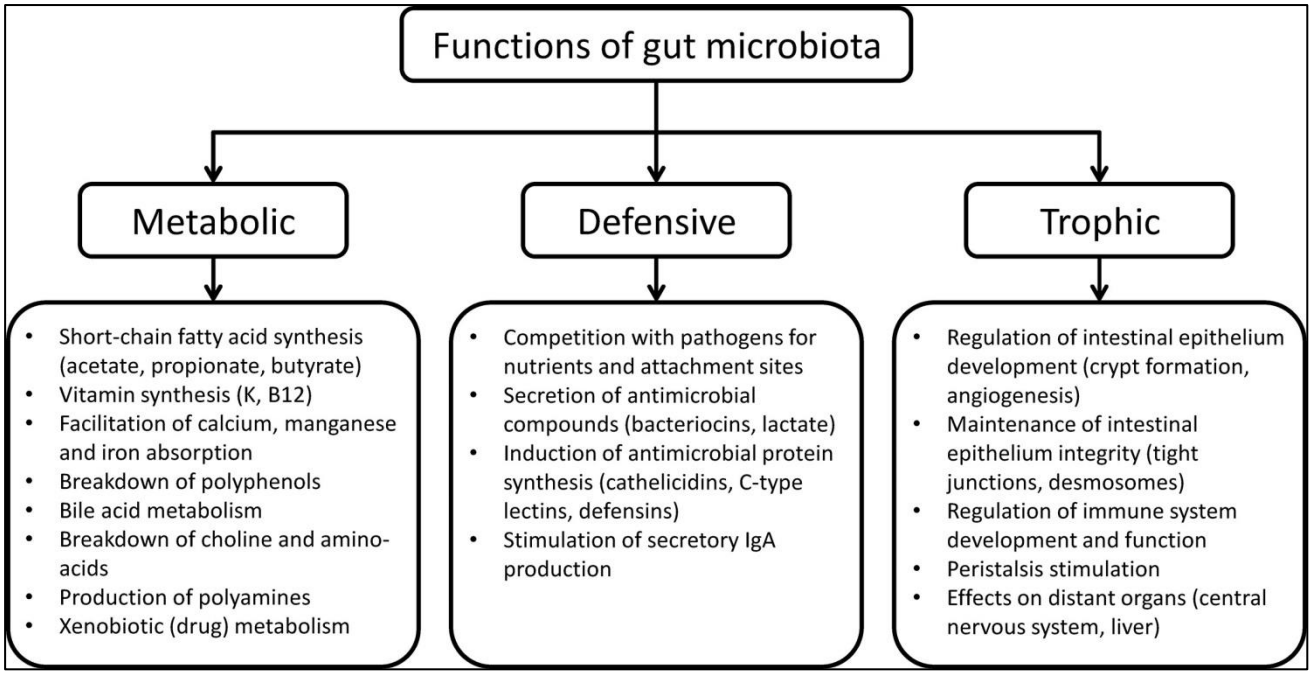


Fig. 14 Categories of human gut microbiota functions (Ramirez et al., 2020).

3. 3. 1. Nutrient metabolism

Gut microbiota nutritional function is linked to the fermentation of non-digestible dietary fibers and the anaerobic peptide and protein conversions, as a consequence of which the host recovers metabolic energy. Non-digestible dietary fibers and endogenous intestinal mucus fermentation encourages the growth of specialized microbes that produce gases and short chain fatty acids (SCFAs) (**Kovatcheva-Datchary et al., 2013**; **Valdes, 2018).**

The major SCFAs produced are acetate, propionate, and butyrate. Acetate, the amplest SCFA, is essential other bacteria growth and it involves in cholesterol metabolism and lipogenesis. Propionate regulates gluconeogenesis and satiety signaling after being transferred to the liver, while Butyrate represents human colonocytes main energy source, and has beneficial effects on energy homeostasis and glucose, it could also induce colon cancer cells apoptosis, and activate, intestinal gluconeogenesis **(Thursby and Juge, 2017; Valdes, 2018).**

3. 3. 2. Immunological role of gut microbiota

To defend against pathogens, the intestinal microbiota performs a number of immune system-related roles **(Thursby and Juge, 2017; Shabana et al., 2018),** It influences the development of lymphatic tissue and prevents bacterial overgrowth and infection by forming an ecological barrier for colonization, inducing IgA and antimicrobial protein production in the host, and competing for attachment sites and nutrients with indigenous pathogenic fungi or bacteria **(Laukens et al., 2016; Ramirez et al., 2020),** It is also involved in the development and maturation of the immune system (**Amon and Sanderson, 2017**; **Kovatcheva-Datchary et al., 2013**). Furthermore, proper immune function depends on the interaction between commensal microbiota and the mucosal immune system (**Fig. 15**) **(Thursby and Juge, 2017).**

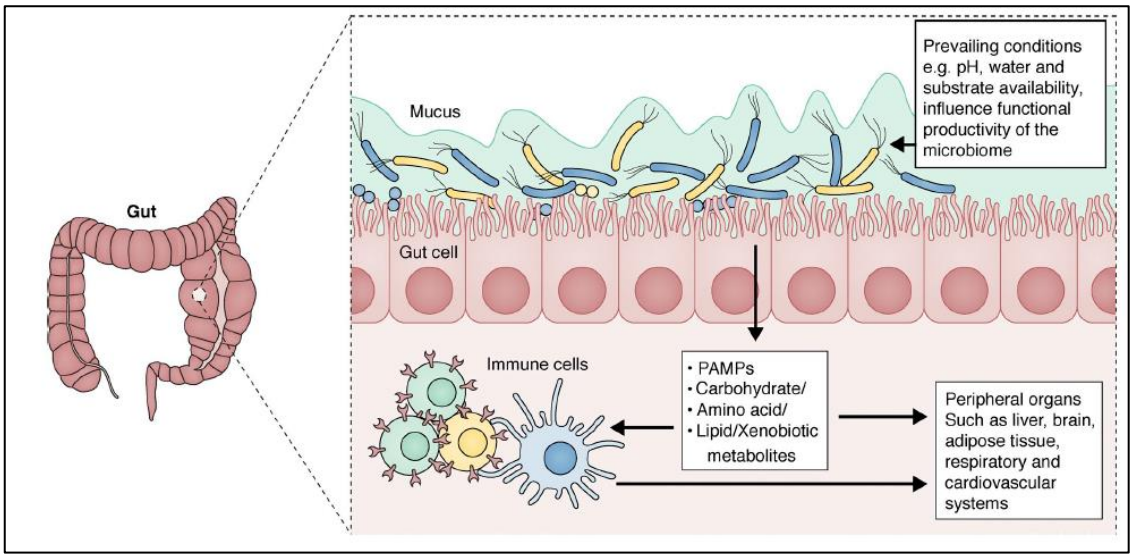


Fig. 15 The mutual symbiosis of the gut microbiota with its host. PAMPs= pathogen-associated molecular patterns (Durack and Lynch, 2018).

The loss of microbial diversity in the gut microbiome, particularly a reduction in the number of specific bacteria species that promote immune tolerance, has been linked to a number of chronic diseases, including gastrointestinal inflammatory and metabolic disorders, as well as neurological, cardiovascular, and respiratory issues. Aside from that, the presence of certain bacteria has been related to the progression of certain complex diseases, such as Prevotella in reactive arthritis **(Durack and Lynch, 2018; Scher et al., 2013).** The gut microbiota's function in health and disease is illustrated in **(Fig. 16).**

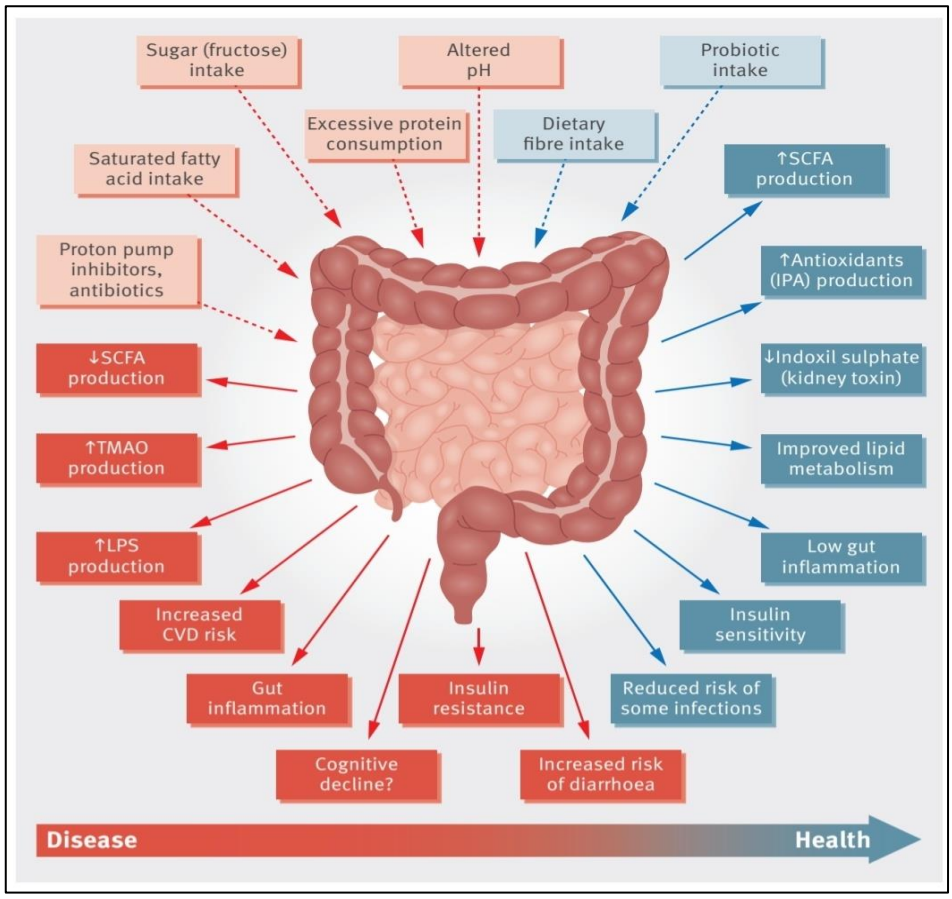


Fig. 16 The gut microbiota's function in health and disease is depicted schematically with some examples of inputs and outputs. CVD=cardiovascular disease; IPA=indolepropionic acid; LPS=lipopolysaccharide; SCFA=short chain fatty acids; TMAO=trimethylamine N-oxide (Valdes, 2018).

4. Influences on the gut microbiota

The composition of the human gut microbiome is characterized by notable variability from person to another, but it is influenced by many common nonmodifiable and modifiable factors. These factors include: mode of infant delivery and feeding, geography, stress, antibiotics, sex, the aging process, genotype, and diet **(Fig. 17) (Cresci and Bawden, 2015; Deschasaux et al., 2018; Lane and Yadav, 2020).**

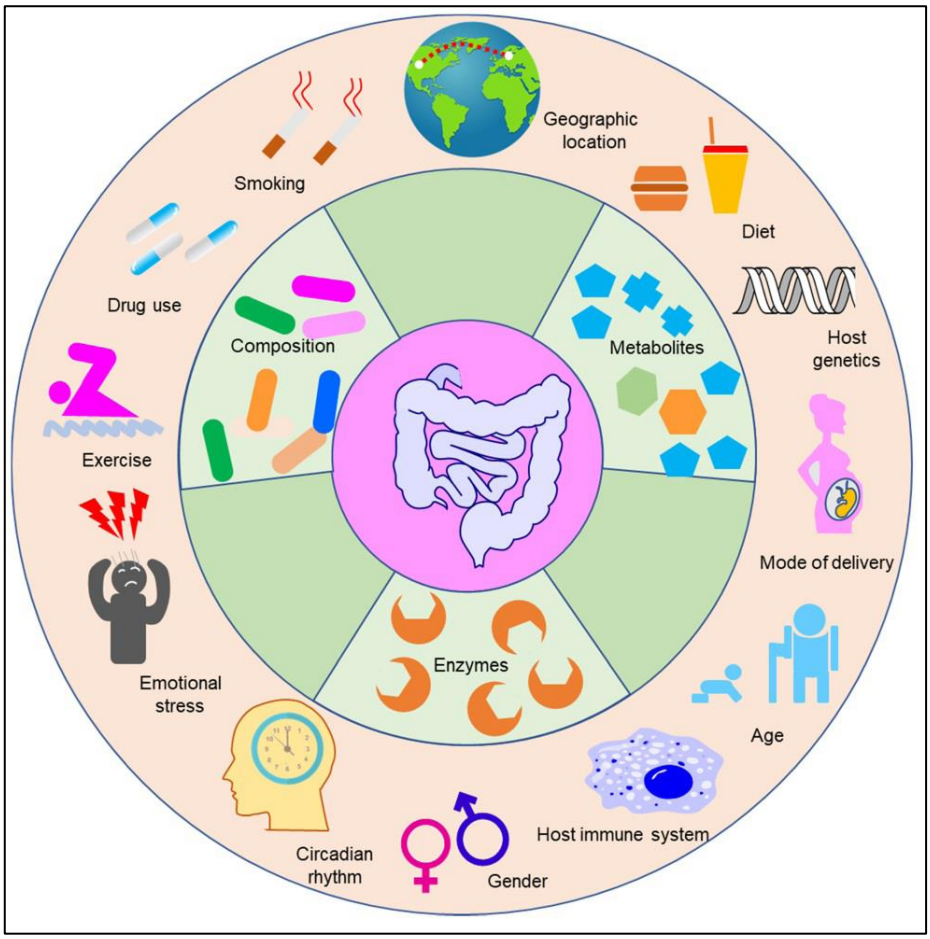


Fig. 17 The factors influencing the composition and function of gut microbiota (Feng et al., 2020).

4. 1. Mode of infant delivery

The early-life microbiome is affected by mode of delivery. In fact, the composition of the infant's gut microbiota is initially defined by the source of the newborn's first microbial inoculum **(Arrieta et al., 2014; Cresci and Bawden, 2015).** Studies have shown a variety in the structure of the gut community between infants delivered via cesarean section (C-section, CS) and vaginally delivered infants (VD) (**Mitchell et al., 2020).** Children born vaginally harbored more *Bifidobacterium* and *Bacteroides spp.* with a reduction of *Enterococcus* and *Klebsiella spp* compared to cesarean born infants **(Fig. 18) (Cresci and Bawden, 2015; Reyman et al., 2019).**

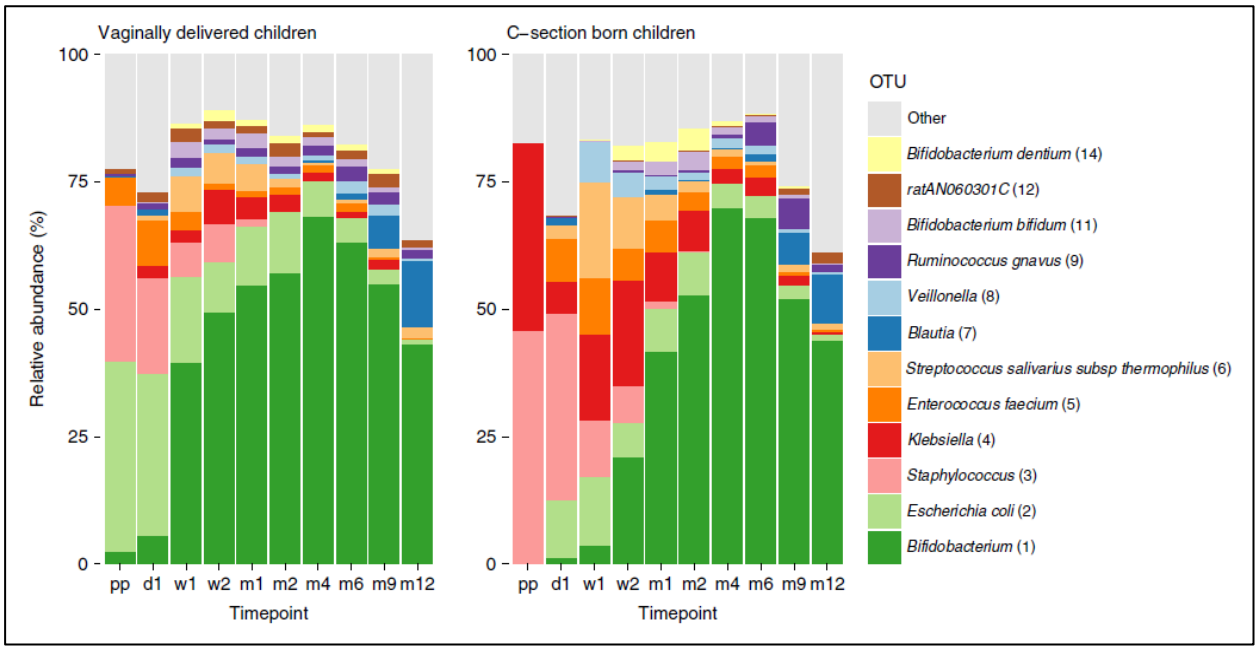


Fig. 18 Impact of delivery mode on early life microbial composition. OTU= Operational Taxonomic Unit, Pp = postpartum, d =day, m= month (Reyman et al., 2019).

4. 2. Infant feeding method

As infants grow, feeding methods play an essential role in the development of their gut bacteria (**Mitchell et al., 2020)**. It has been reported by many researchers that human breast milk, besides its immunological components like immunoglobulins, cytokines, growth factors, and microbiologic factors, contains more than 600 species of bacteria. It includes several beneficial genera of Bifidobacterium, as well as some skin bacteria such as Streptococci and Staphylococci that transfer from the mother's skin during suckling **(Cresci and Bawden, 2015; Wen and Duffy, 2017; Moore and Townsend, 2019).** Additionally, breast milk is rich in prebiotics, such as oligosaccharides, which support the beneficial Bacteriodetes within the GIT **(Cresci and Izzo, 2017; Stinson et al., 2018).**

Comparisons between breast-fed and formula-fed infants show that breastfeeding is associated with higher levels of *Bifidobacteria* and *Lactobacillus,* whereas the gut of formula-fed infants is dominated by *Bacteroides*, *Clostridium*, *Streptococcus*, *Enterobacteria*, and *Veillonella* spp **(Arrieta et al., 2014; Stewart, 2018).**

4. 3. Geography

The diversity and composition of gut microbiota can also be affected by ethnicity and geographic location, which can alter both the repertoire of bacterial species within the gut and their abundance **(Arrieta et al., 2014; Cresci and Bawden, 2015).** Geography is the combination of genetic, environmental and cultural factors that changes from an ethnogeographic population to another, it is thought to affect the microbiota based on the regional lifestyle **(Arrieta et al., 2014; Gupta et al., 2017).**

As illustrated in figure 19, ethnicity explains the large variation in the gut microbiota composition between individuals. It has been demonstrated that Prevotella enterotype is increased in the guts of Moroccans, Turks and Ghanaians, while Bacteroides enterotype is common in Western countries, Africa and South Asia **(Fig. 19)** (**Deschasaux et al., 2018; Senghor et al., 2018).**

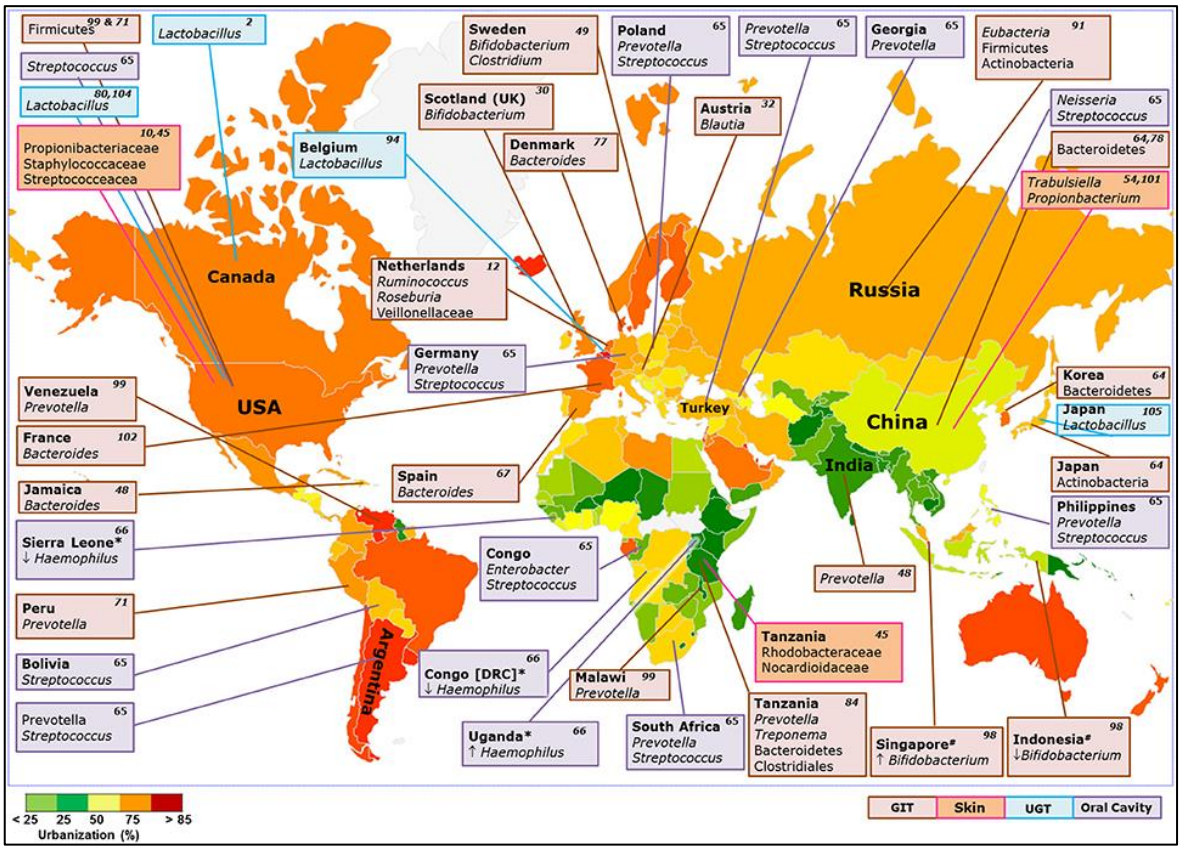


Fig. 19 Enriched taxa at various niches of the human body in diverse populations around the world (Gupta et al., 2017).

4. 4. Stress

Stress can disrupt the gut homeostasis; it modulates both the structure and activity of the gut microbiota community. This demand can be induced by physical (e.g., environmental temperature), physiological (e.g., altered glucose levels), or psychological stressor (e.g., social defeat) **(Mackos et al., 2017; Molina-Torres et al., 2019).**

As a response to the presence of stressful stimulus, the hypothalamic- pituitary-adrenal (HPA) gets activated. This results in the release of behavior-altering chemicals including glucocorticoids (cortisol), catecholamines, and other hormones which can contribute to stressor-induced changes in immune and GI function **(Fig. 20) (Cresci and Bawden, 2015; Karl et al., 2018).** According to **Kelly et al. (2015)**, stress has profound effects on the gut permeability and the developmental trajectory of the intestinal barrier, due to corticotrophin releasing factor (CRF) and its receptors (CRFR1 and CRFR2), play a key role in stress-induced gut permeability dysfunction.

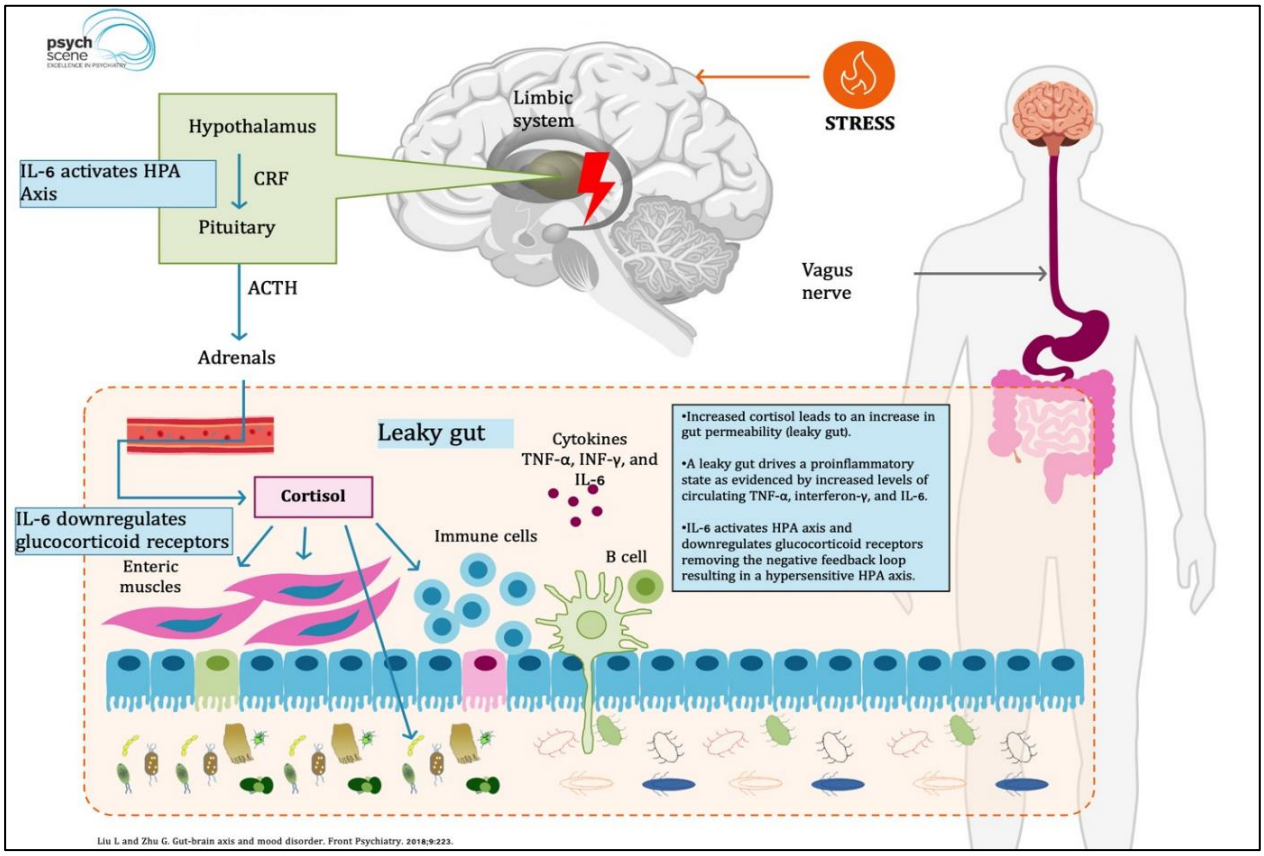


Fig. 20 The impact of stress on gut microbiota (Net 04).

4. 5. Antibiotics

Antibiotics are administered to target pathogenic bacteria; although, due to their broad-spectrum activities, related members of the microbiota are also killed or inhibited **(Cresci and Bawden, 2015; Feng et al., 2020).**

As a side effect, antibiotic treatment can affect the gut microbiota community by causing a decreased in their diversity and richness **(Thursby and Juge, 2017).** This includes loss of specific populations of microbiota, that leads to the alteration of metabolites; increases gut susceptibility to colonization; and induces the development of bacterial antibiotic resistance **(Zhang and Chen, 2019; Ramirez et al., 2020).** Besides that, antibiotics also shape the physiology and gene expression of the active human gut microbiome and affect protein activity and overall metabolism of the gut microbiota, which can cause numerous potential diseases as it is shown in **Fig. 21 (Francino, 2016; Thursby and Juge, 2017).** However, **Schwartz et al. (2020)** have reported that antimicrobial agents can have different effects on the gut microbiota, depending on the state of the microbiome at the time of perturbation and the strength of the perturbation (route, spectrum, and duration of antibiotics).

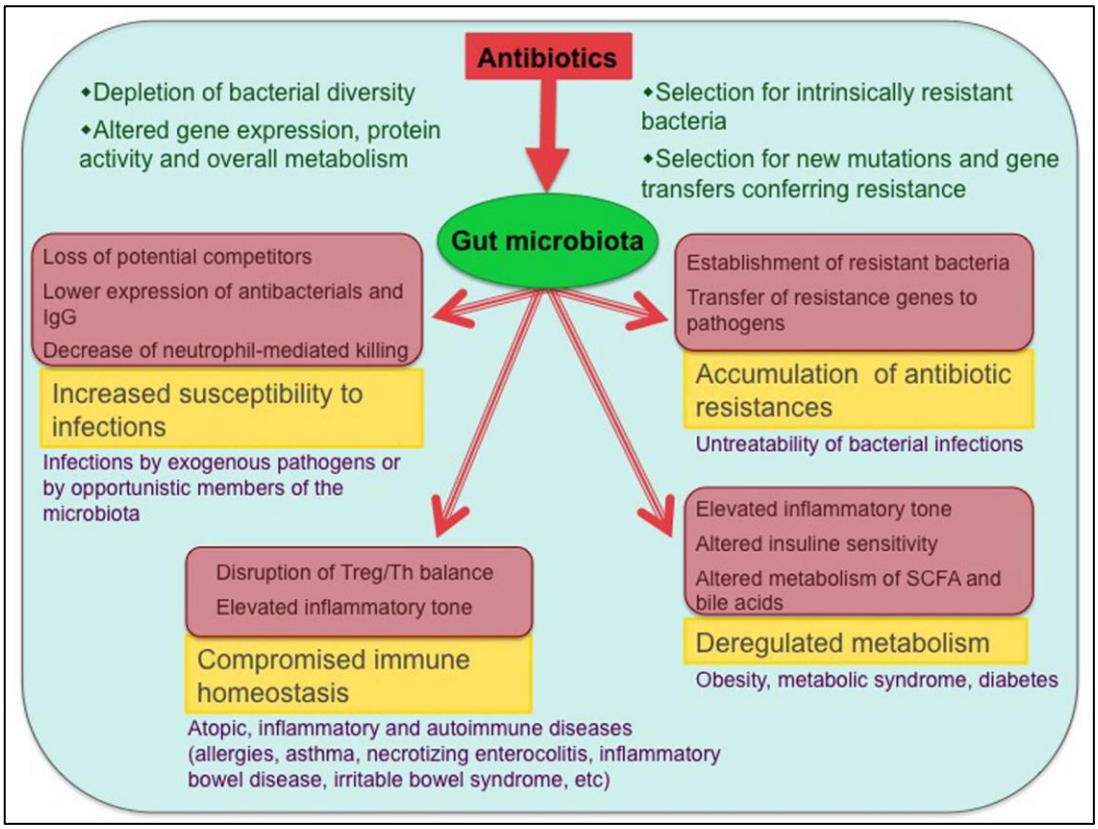


Fig. 21 Antibiotic effects on the gut microbiota and associated health problems (Francino, 2016).

Once the use of antibiotics has ceased, the dysbiosis can remain after long periods of time, extending months and even years. Antibiotic-induced microbiota alterations leaves a lasting negative effect on the gut microbial community, especially in early life **(Cresci and Bawden, 2015; Francino, 2016; Ishiguro et al., 2018).**

Chapter two: Nutrition modulates the microbiota

Chapter two: Nutrition modulates the microbiota

Our dietary patterns are based on foods that include important elements for our bodies, such as proteins, lipids, carbohydrates, vitamins, and minerals, which are the main significant determinants and major source of energy for the microbial environment in the gastrointestinal tract **(Del Chierico et al., 2014; Moco and Ross, 2014; Senghor et al., 2018).** Food is considered a critical component that might affect the gut microbiota that serves as a link between it and human health promotion and modulation **(Fig. 22) (Wu et al., 2019)**.

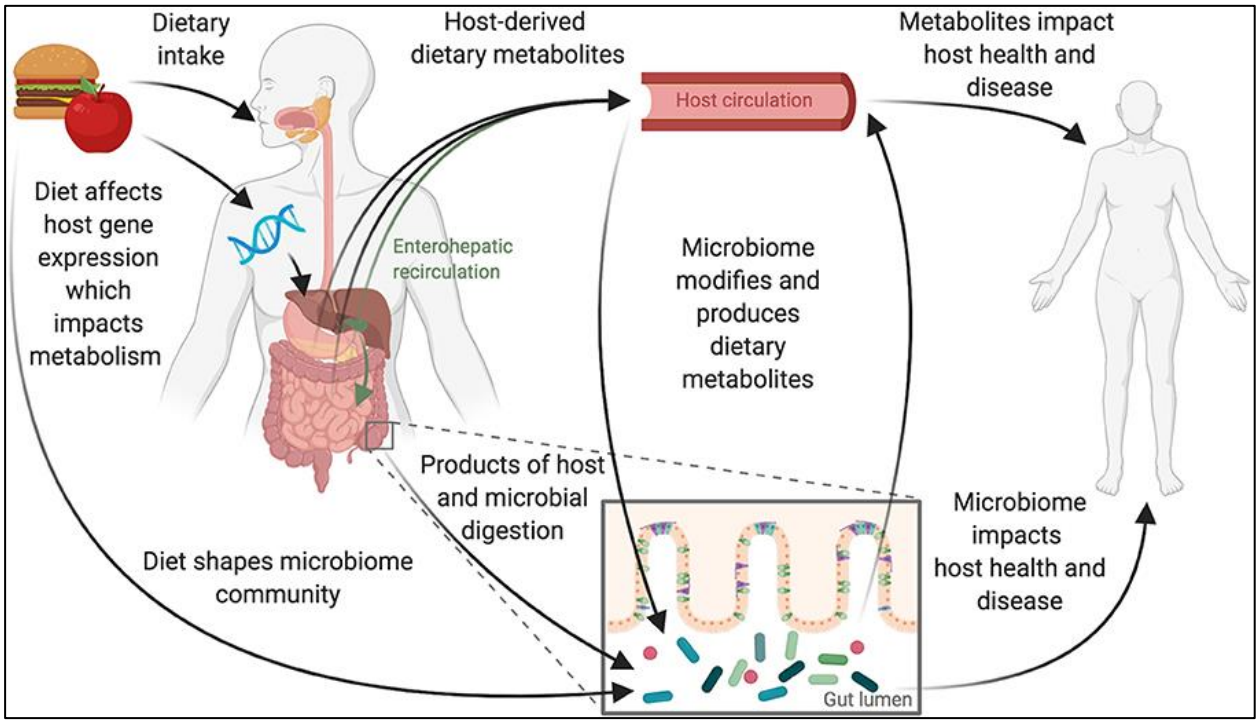


Fig. 22 Impact of diet on the gut microbiome and human health (Johnson et al., 2020).

1. Macronutrients

The gut microbiota composition and activity are known to be influenced by the overall balance of macronutrients carbohydrate, protein, and fat that are not digested and absorbed by the human digestive system **(Danneskiold-Samsøe et al., 2018; Azcarate-Peril et al., 2019)**.

1. 1. Carbohydrates

Carbohydrates are the most well-studied dietary components in connection to the modulation of the human gut microbiota since they are the primary source of

energy for both humans and our colonic microorganisms. **(Conlon and Bird, 2014; Ishiguro et al., 2018).** Carbohydrates in human diets have a variety of effects on the GM depending on their type, they range from simple sugars to starch and NSPs, and were categorized into digestible and indigestible substrates **(Fig. 23) (Leong et al., 2019; Rinninella et al., 2019; Ramos and Martín, 2020).**

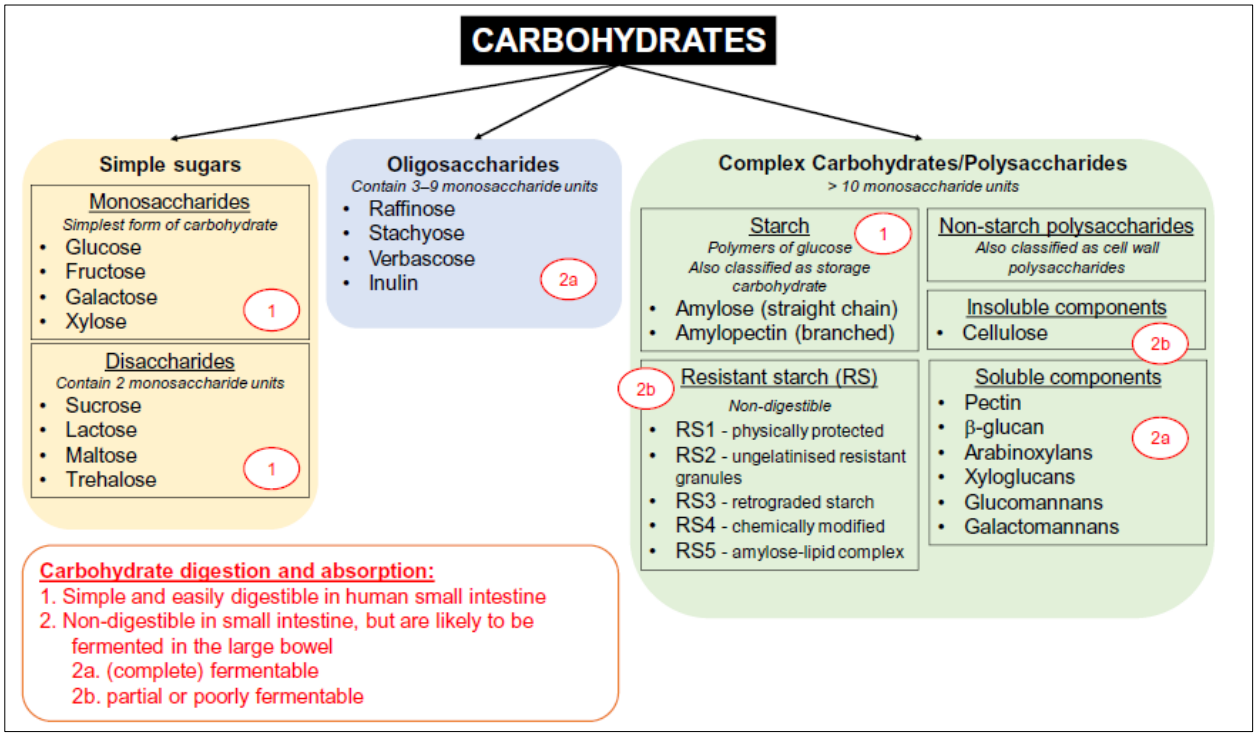


Fig. 23 Dietary carbohydrates and their potential for digestion and absorption in human body (Leong et al., 2019).

Monosaccharides (e.g., glucose) and disaccharides (e.g., sucrose or lactose) are classified as digestible carbohydrates, they are completely absorbed in the small intestine where they tend to increase Bifidobacteria while decreasing Bacteroides **(Table 2) (Moco and Ross, 2014; Danneskiold-Samsøe et al., 2018; Seo et al., 2020).** However, complex undigested carbohydrates, so-called "dietary fiber", are resistant to digestion in the small intestine, and reach the large intestine where they are fermented by the colonic bacteria. Fermentation of these compounds leads to the generation of short-chain fatty acids (SCFAs) and consequently providing numerous health benefits **(Leong et al., 2019; Rinninella et al., 2019; Ramos and Martín, 2020).**

Non-digestible carbohydrates are also referred to as microbiota-accessible carbohydrates (MACs), they include non-starch polysaccharides, lignin, resistant starches, and non-digestible oligosaccharides (**Ishiguro et al., 2018; Rinninella et al., 2019).** Zhang et al., **(2020)** observed that low starch consumption could be favorable to gut structure by altering GM diversity, beneficial bacteria quantity, and lactic acid content **(Fig. 24)**. Resistant starch was reported to enhance the abundance of *Bifidobacterium adolescentis, Ruminoccocus bromii, Eubacterium rectale,* and *Parabacteroides distasonis* **(Table 2) (Seo et al., 2020).**

Table 2. Alterations of gut microbiota associated with carbohydrates (Seo et al., 2020).

Types of Carbohydrates	Details	Effects on Gut Microbiota
Mono- and disaccharides	Daily fruits	Bifidobacteria ↑ Bacteroides ↓
	Lactose	Clostridia ↓ Lactobacilli ↑
	Lactose	Production of SCFAs ↑
Nondigestible carbohydrates	Fruits and vegetable fibers FODMAP [1]	Microbial richness and biodiversity ↑
	FODMAP [1] Galactooligosaccharides Resistant starch type 4 Whole-grain cereals Fructo-oligosaccharide	Bifidobacteria ↑
	Resistant starch type 4	Actinobacteria ↑ Bacteroidetes ↑ Firmicutes ↓
	Resistant starch type 2	Ruminococcus ↑
	Resistant starches Resistant starch type 2	Ruminococcus ↑ Eubacteria ↑
	Resistant starches Resistant starch type 4 Whole-grain cereals	Eubacteria ↑ Parabacteroides ↑ Lactobacilli ↑
	Oligosaccharides mixture [2] Polysaccharide peptides	Clostridia ↓
	Polydextrose Polysaccharide peptides Fructo-oligosaccharide	Enterococcus ↓
	Long-term high fiber diet	Production of SCFAs ↑

[1] Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. [2] Mixture of short-chain galactooligosaccharides, long-chain fructooligosaccharides, and pectin-hydrolysate-derived acidic oligosaccharides.

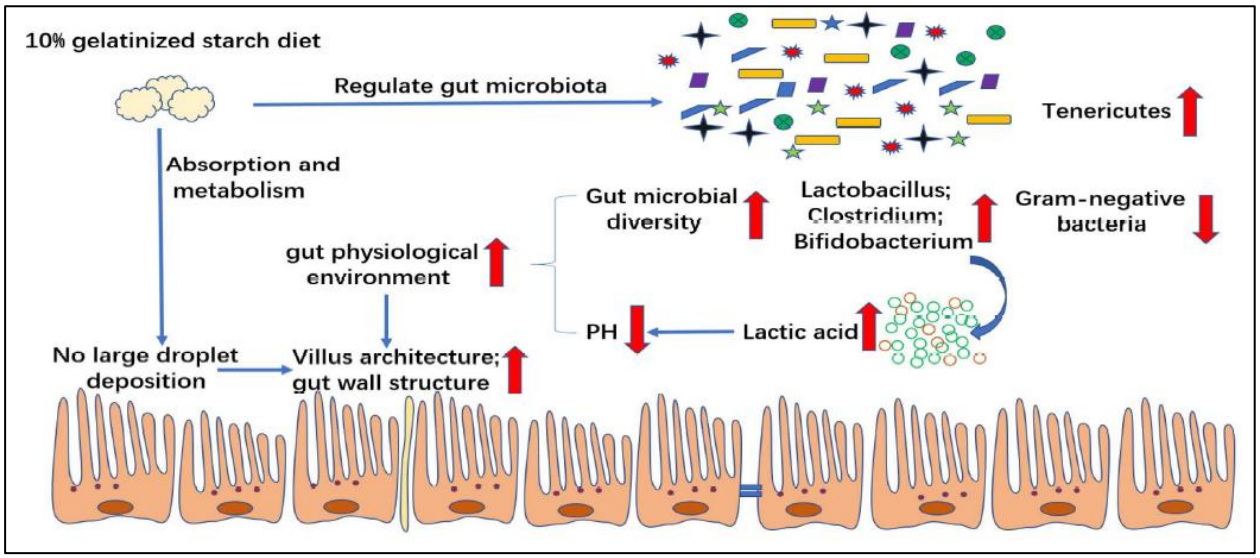


Fig. 24 Mechanism by which 10% gelatinized starch diet influence the gut health (Zhang et al., 2020).

MACs have the ability to influence gut microbial homeostasis by modifying its composition and activity, which can enhance the development of inflammatory illnesses as asthma, infections, and inflammatory bowel disease **(Daïen et al., 2017; Danneskiold-Samsøe et al., 2018).**

1. 2. Proteins

Proteins have different effects on gut microbiota composition depending on their sources. The majority of protein sources come from plants (vegetables, starchy foods, nuts…) or animals (meat, fish, poultry, dairy foods…) **(Senghor et al., 2018; Zhao et al., 2018; Rinninella et al., 2019)**.

A study has demonstrated that the consumption of animal-based proteins is highly associated with an increase in the abundance of bile-tolerant anaerobes such as Bacteroides, Alistipes, and Bilophila, while the *Bifidobacterium adolescentis* presents the reverse association for this type of proteins as illustrated in **Fig. 25 (Singh et al., 2017; Rinninella et al., 2019)**. These changes in the gut microbiota cause an increase in trimethylamine oxide (TMAO) in the liver, a toxin that is

reported to be associated with high risk for atherosclerosis development and has recently been linked to obesity **(Madsen, 2017; Danneskiold-Samsøe et al., 2018)**.

Vegetable proteins such as whey and pea proteins, on the other hand, enriched operational taxonomic units belonging to Bifidobacterium and Lactobacillus communities, and reduced pathogenic *Bacteroides fragilis* and *Clostridium perfringens* **(Fig. 25) (Singh et al., 2017; Ramos and Martín, 2020).**

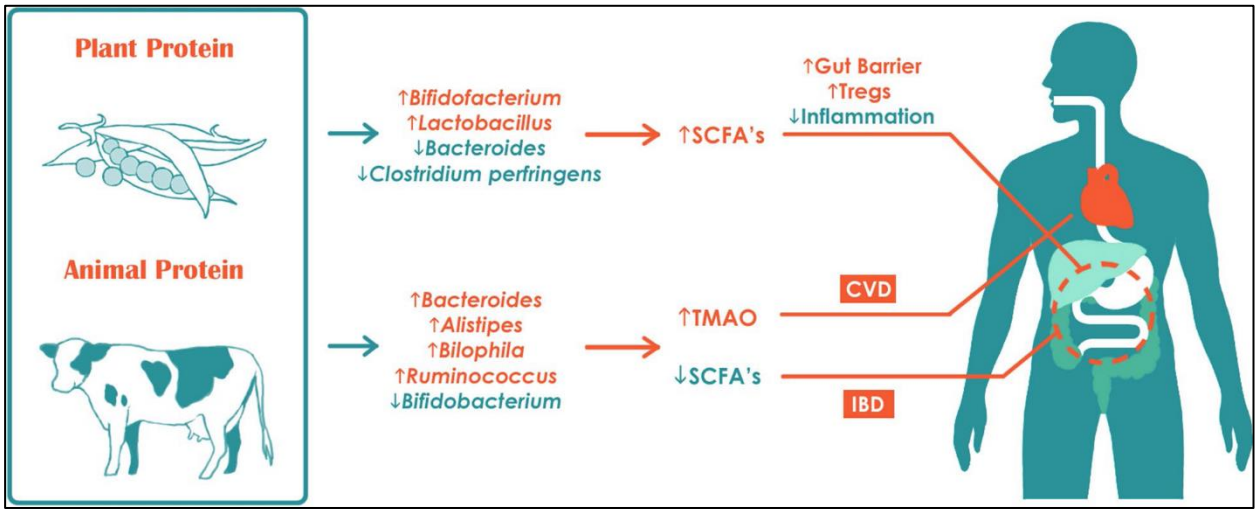


Fig. 25 Impact of dietary protein on intestinal microbiota and health outcomes. *SCFA's* short chain fatty acids, *TMAO* trimethylamine N-oxide, *Tregs* T regulatory cells, *CVD* cardiovascular disease; *IBD* inflammatory bowel disease (Singh et al., 2017).

Compared to animal proteins, plant proteins improve the metabolism and intestinal equilibrium **(Danneskiold-Samsøe et al., 2018)**. For example: pea protein increases intestinal SCFA levels, which are anti-inflammatory and crucial for the mucosal barrier's maintenance **(Singh et al., 2017).**

1. 3. Fat

While changes in carbohydrate and protein diet have been shown to influence the composition of the gut microbiota, the effect of fats is less well understood. However, multiple studies have shown that the composition and metabolic activity of the gut microbiota are influenced by the quantity and quality of dietary lipids **(Conlon and Bird, 2014; Danneskiold-Samsøe et al., 2018; Ishiguro et al., 2018)**.

According to the presence of double bonds between carbon molecules, dietary fatty acids can be classified as saturated (SFAs), monounsaturated (MUFAs), or

polyunsaturated fatty acids (PUFAs). SFAs are primarily found in animal products, whereas unsaturated fatty acids, including omega-3 and omega-6 acids, are found in plant-based lipids **(Rinninella et al., 2019; Ramos and Martín, 2020). Fig. 26** shows an overview of the changes in the gut microbial profile with differences in animal and plant-based fat sources.

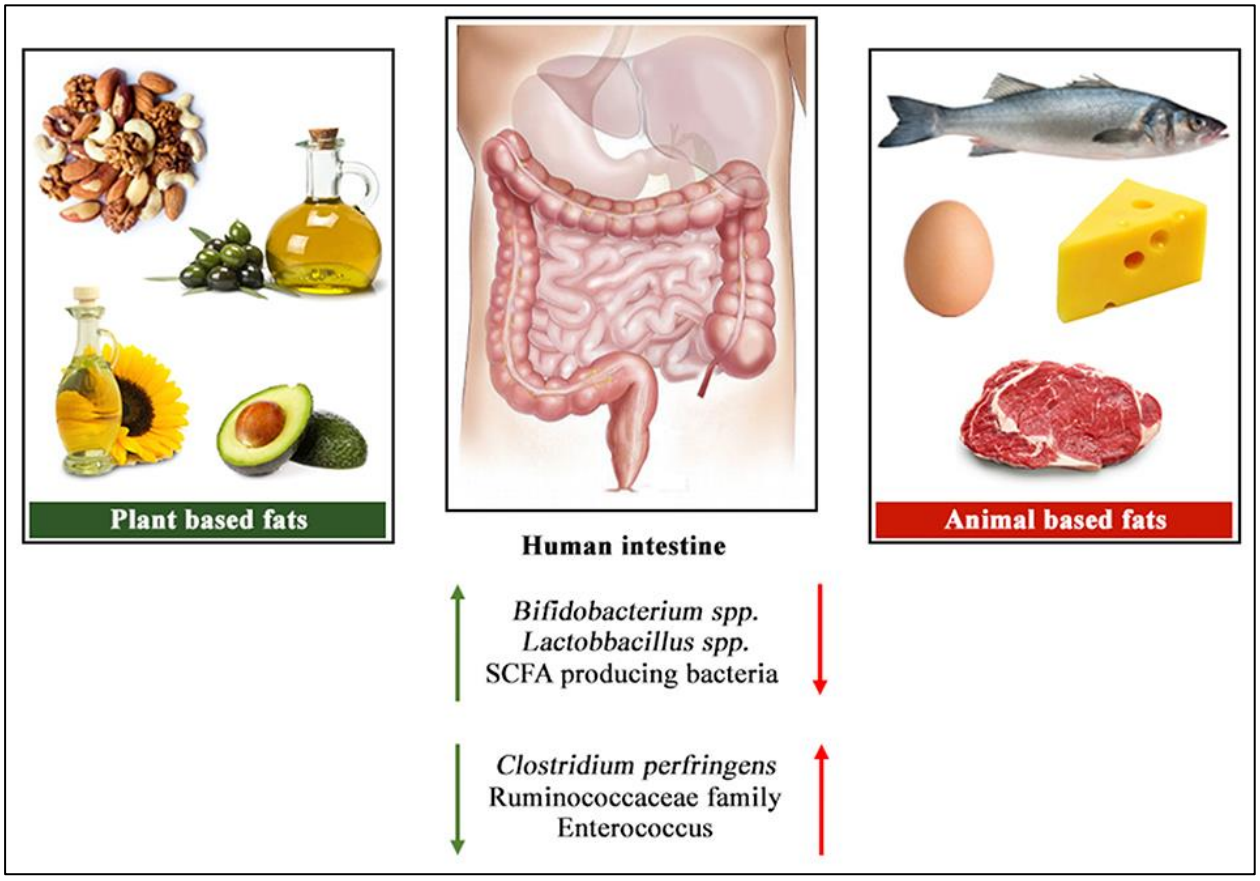


Fig. 26 Overview of the changes in the gut microbial profile with differences in animal and plant-based fat sources (Muralidharan et al., 2019).

Saturated fatty acids (SFA) appear to reduce Bacteroides, Prevotella, Lactobacillus spp., and Bifidobacterium spp., while promoting pro-inflammatory Bilophila development leading to intestinal dysbiosis. Unsaturated plant-based lipids, on the other hand, diminish harmful bacteria while increasing the prevalence of Bifidobacterium and butyrate-producing bacteria in the gut **(Coelho et al., 2018; Rinninella et al., 2019; Ramos and Martín, 2020).**

2. Micronutrients

Aside from macronutrients, many studies suggest that micronutrients, such as unabsorbed vitamins and minerals that reach the colon, can offer vital energy and nutrition to a variety of bacteria, thus playing an important role in shaping the GM. **(Karl et al., 2018; Ramos and Martin, 2020)**. The sources of colonic micronutrients are either the diet **(Fig. 27)** or gut microbial production. Minerals can only be obtained from diet, while some vitamins, such as vitamin K2 and water-soluble B-vitamins (folic acid, niacin, biotin, cobalamin…), can be generated in insufficient amounts by various components of the intestinal bacteria. **(Zhang et al., 2018; Kundra et al., 2020; Vernocchi et al., 2020).**

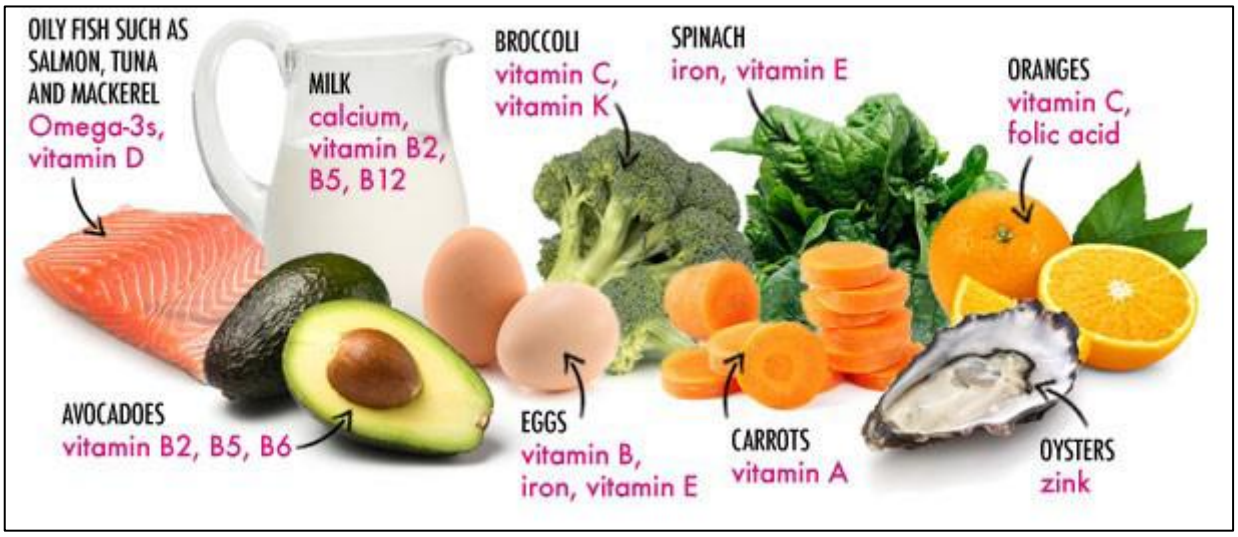


Fig. 27 Foods considered to be rich sources of micronutrients (Teferra, 2015).

2. 1. Vitamins

Vitamin C is the most essential antioxidant, which can only be gotten through food (mainly fruits and vegetables). This vitamin can considerably modulate the gut microbiota, consequently improving gut dysbiosis and health. According to studies, VC consumption increased Firmicute enrichment while negatively affecting Bacteroidetes relative abundances **(Spisni et al., 2020; Li et al., 2021).** Other antioxidant vitamins, such as carotenoids (e.g., Lutein), may have an impact on the composition of the gut microbiota. It was shown that lutein enhanced the development of Bifidobacteria and Lactobacilli while reducing the populations of Bacteroides spp. and Clostridium spp **(Rinninella et al., 2019)**.

Furthermore, human researchers have found strong links between vitamin D and health maintenance due to alterations in the microbiota. Supplementing with vitamin D enhances the relative abundance of beneficial bacteria like Bacteroides and Parabacteroides, while decreasing the abundance of Prevotella **(Ramos and Martin, 2020; Yamamoto and Jørgensen, 2020; Yang et al., 2020).** Vitamin A, on the other hand, has been shown to alter the microbiota indirectly through influencing host-microbe interactions. While acute vitamin A insufficiency increases the abundance of *Bacteroides vulgatus*, this vitamin is able to influence health-beneficial bacteria of the genera Bifidobacterium, Lactobacillus, and Akkermansia **(Zhang et al., 2018; Kundra et al., 2020; Yang et al., 2020).**

Consequently, under some circumstances, the vitamins listed above, as well as a variety of others, may be beneficial to health by targeting gut microbial communities via direct and indirect mechanisms **(Fig. 28) (Steinert et al., 2019).**

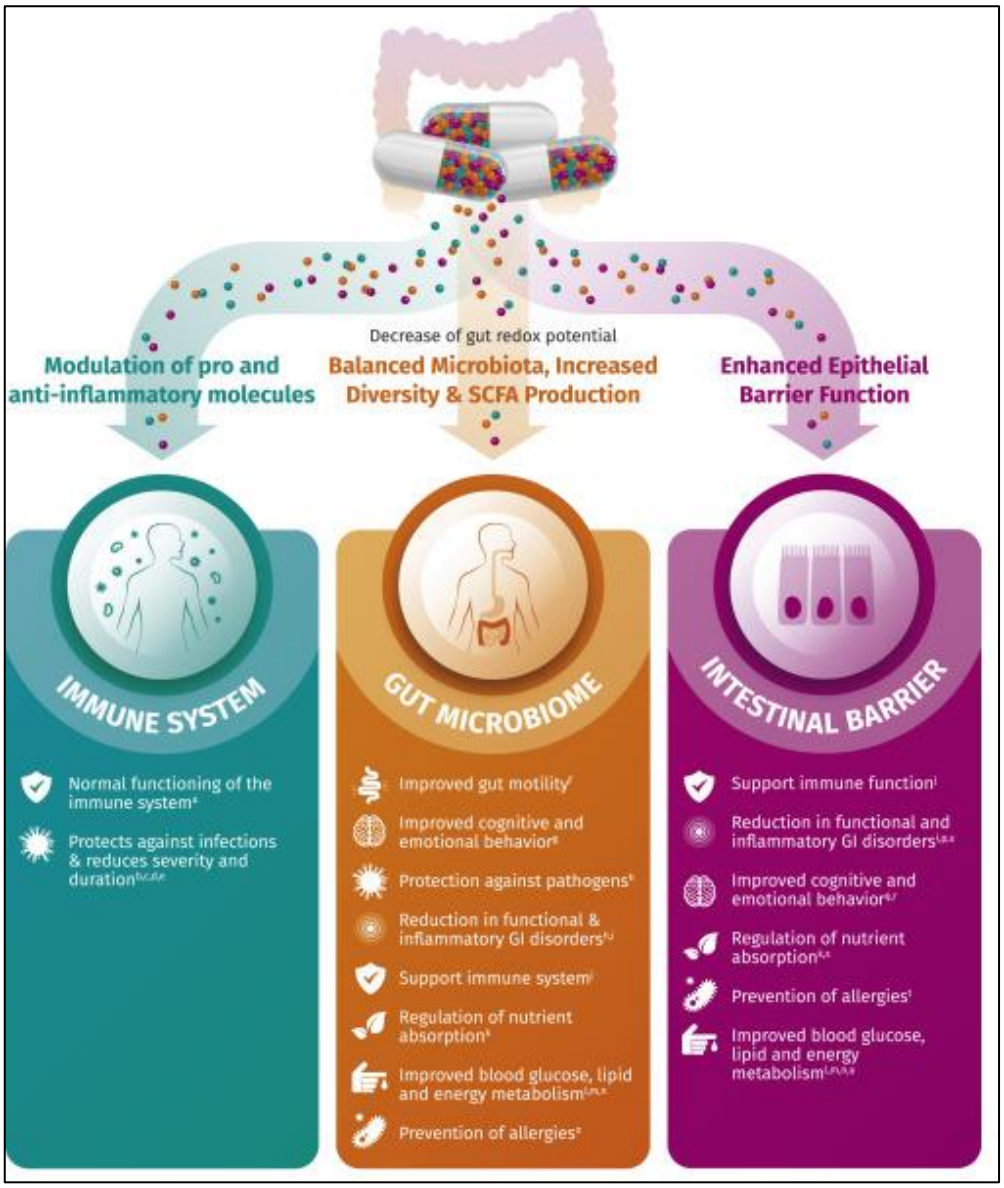


Fig. 28 Colon-Targeted Vitamin Supplementation Potentially Impacts Host Health via Three Interrelated Routes. (1) Direct effects on the gut immune system (left panel). (2) Direct effects on the gut epithelial barrier (right panel). (3) Effects on the gut microbiome and subsequently on gut immune and epithelial barrier via microbial metabolites (middle) **(Steinert et al., 2019).**

2. 2. Minerals

Minerals, like vitamins, have a role in a variety of bacterial physiological activities that affect the gut microbiota. Iron and zinc have been examined the most in terms of how mineral intake affects the gut microbiota **(Karl et al., 2018; Rinninella et al., 2019)**.

Consumption of high-iron formula alters the beneficial and potentially pathogenic microbiota, and it is linked to negative effects on GM, including a

decrease in the relative abundance of Bifidobacterium and Lactobacillus **(Ramos and Martin, 2020; Yang et al., 2020).** Karl et al. **(2018)** reported that heme-rich diet has been demonstrated to increase the abundance of pro-inflammatory Enterobacteriaceae and pathogenic Salmonella, while decreasing the abundance of beneficial taxa such as Lactobaciulls, Roseburia, and *Eubacterium rectale.* Similarly, Zinc deficiency and supplementation seem to affect the gut microbiota structure and the host defense, it was shown that it increases susceptibility to Clostridium difficile infection **(Kundra et al., 2020)**.

Other minerals like calcium, magnesium, phosphorus, and selenium have demonstrated to have minor impacts in supporting healthy gut bacteria including Akkermansia, Bifidobacterium, and Ruminococcus. However, manganese was observed to enhance the growth of several bacterial pathogens such as *Staphylococcus aureus and* Enterococcus faecalis **(Zmora et al., 2019; Kundra et al., 2020; Yang et al., 2020).**

After discussing the impact of micro and macro nutrients on modulating the gut microbiota, we would like to summarize, in **Fig. 29**, the important effects of some nutrients on intestinal microbial community and health:

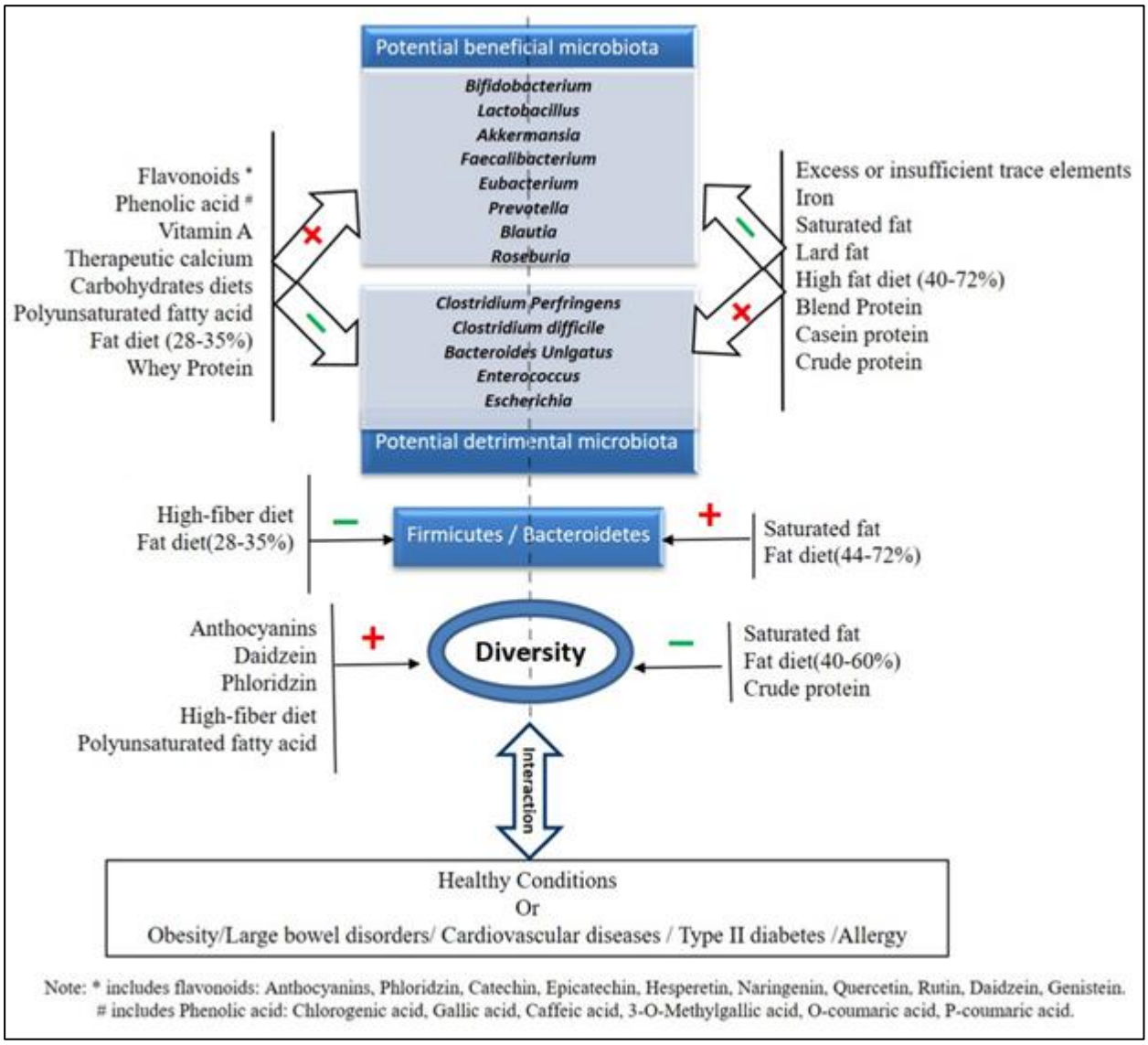


Fig. 29. Effect of micro-and macro-nutrients on potential beneficial or detrimental gut microbiota (Yang et al., 2020).

3. Food

3. 1. Polyphenols

Dietary polyphenols are natural compounds that may also lead to changes in gut microbiota metabolism. Popular foods with a rich content of polyphenols are fruits, vegetables, cereals, tea, coffee, dark chocolate, cocoa powder, and wine **(Fig. 30) (Moco and Ross, 2014; Ishiguro et al., 2018; Kumar Singh et al., 2019).** Polyphenolic compounds, which include flavonoids, secoiridoids, stilbenes, lignans, and phenolic acids, are studied for their antioxidant properties and have been linked with beneficial health claims and prevention of diseases such as cancer and

cardiovascular disease **(Fig. 30) (Conlon and Bird, 2014; Zmora et al., 2019; Sakkas et al., 2020; Spisni et al., 2020).**

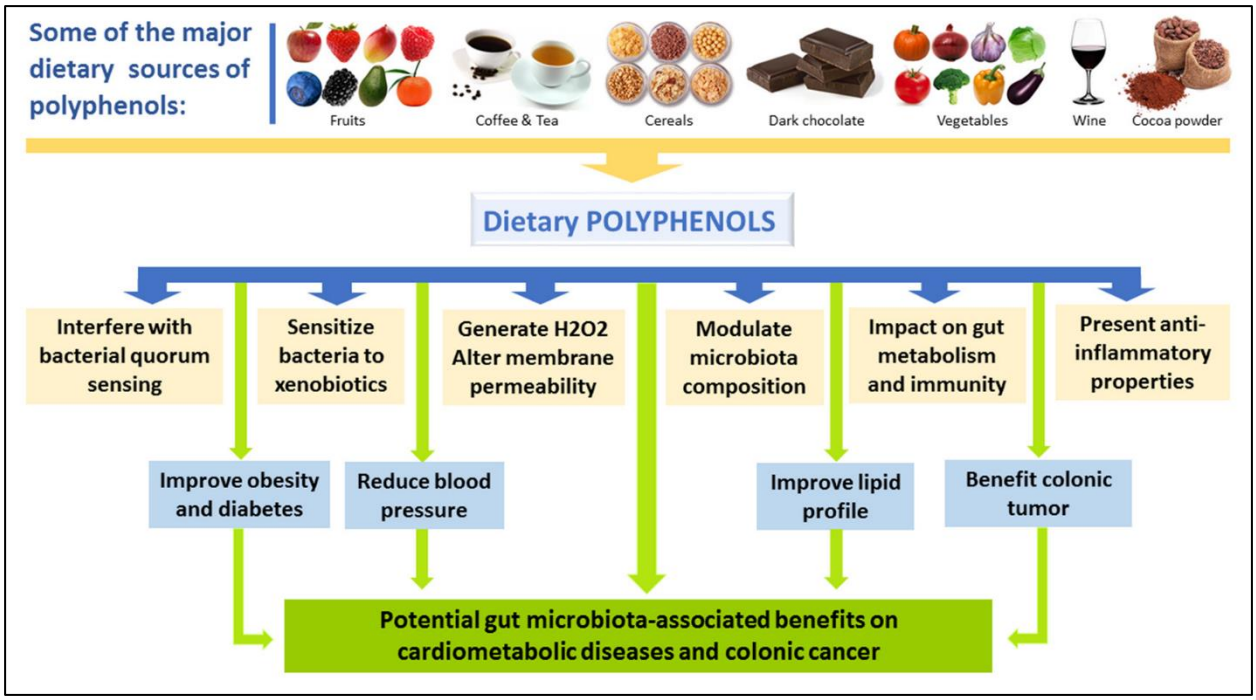


Fig. 30 Major sources of dietary polyphenols and the potential gut microbiota-associated benefits on human health (Kumar Singh et al., 2019).

Unabsorbed polyphenolic compounds and produced metabolites that reach the colon may modulate the GM composition and function, through promoting the growth of beneficial bacteria or inhibiting the development of pathogens **(Ramos and Martín, 2020; Kasprzak-Drozd et al., 2021).** Wild blueberries, for example, have been shown to increase Bifidobacterium and Lactobacillus, which are the commonly enriched bacterial genera due to polyphenols, while tea and red wine polyphenols increases microorganisms such as Klebsiella, and inhibit others such as bifidobacteria, *Blautia coccoides* or Bacteroides **(Fig. 31) (Valdes et al., 2015; Singh et al., 2017; Sakkas et al., 2020).**

A study examining the antibacterial activity of polyphenols found that a decrease in pathogenic *Clostridium perfringens, Clostridium histolyticum, Staphylococcus aureus,* and *Salmonella typhimurium* is probably attributable to the consumption of fruit polyphenols **(Singh et al., 2017; Spisni et al., 2020).** Moreover, other researches confirm that Polyphenols expand the population of

Faecalibacterium prausnitzii and *Akkermansia muciniphila*, both characterized by an anti-inflammatory effect, in addition to *Roseburia* sp., which produces butyrate **(Fig. 31) (Kasprzak-Drozd et al., 2021).**

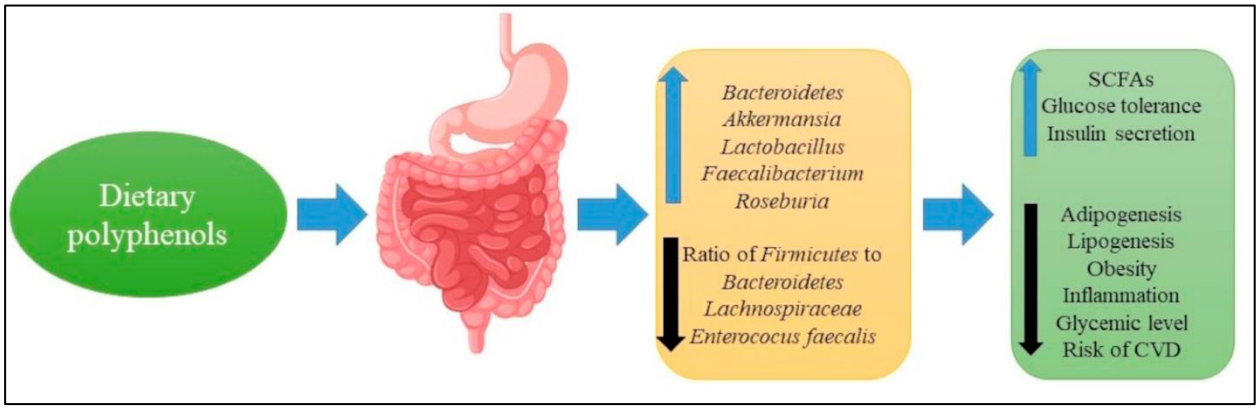


Fig. 31 Influence of the dietary polyphenols on the gut microbiota and possible outcome; SCFAs— short-chain fatty acids (Kasprzak-Drozd et al., 2021).

Table 3. below summarize the main polyphenolic sources that impact the gut microbiota abundances.

Table 3. A summary of the human studies that demonstrate the impact of polyphenols on gut microbiota (Ishiguro et al., 2018).

Phenolic compound	Amount	Impact on microbiome
Green tea (flavanols)	~10 cups/day	Decrease *in Clostridium perfringens* and other *Clostridium* spp., increase in *Bifidobacterium* spp.
Green tea (flavanols)	4 cups/day	Increase in *Bifidobacterium* spp.
Red wine: dealcoholized red wine and red wine	272 mL/day	Increase *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Eggerthella lenta*, and *Blautia coccoides-E. rectale* group

Cocoa	494 mg/day	Increase in *Eubacterium rectale-C. coccoides* group, *Lactobacillus* spp., *Enterococcus* spp., *Bifidobacterium* spp.
Wild blueberry	25 g/day	Increase in *Lactobacillus acidophilus* and *Bifidobacterium* spp.
Soy	100 mg/day of isoflavones aglycon equivalents	Increase in Erec cluster, *Lactobacillus-Enterococcus*, *Faecalibacterium prausnitzii*, and *Bifidobacterium* spp.
Soy milk (26.5% betaconglycinin/ 38.7% glycinin)	500 mL/day	Decreased Firmicutes to Bacteroidetes ratio, increased *Eubacterium* and *Clostridium*, decreased *Bifidobacterium* spp.

3. 2. Food additives

Food additives are synthetic or natural substances added to food to preserve or improve food safety, flavor, color, and texture, which can be affected by oxidation, enzyme activity, and microbe development **(Lu and Zuo, 2018; Cao et al., 2020).** Flavors, colorants, emulsifiers, sweeteners, and thickeners are among the several types of food additives that are shown in **Fig. 32** (**Wu et al., 2019).**

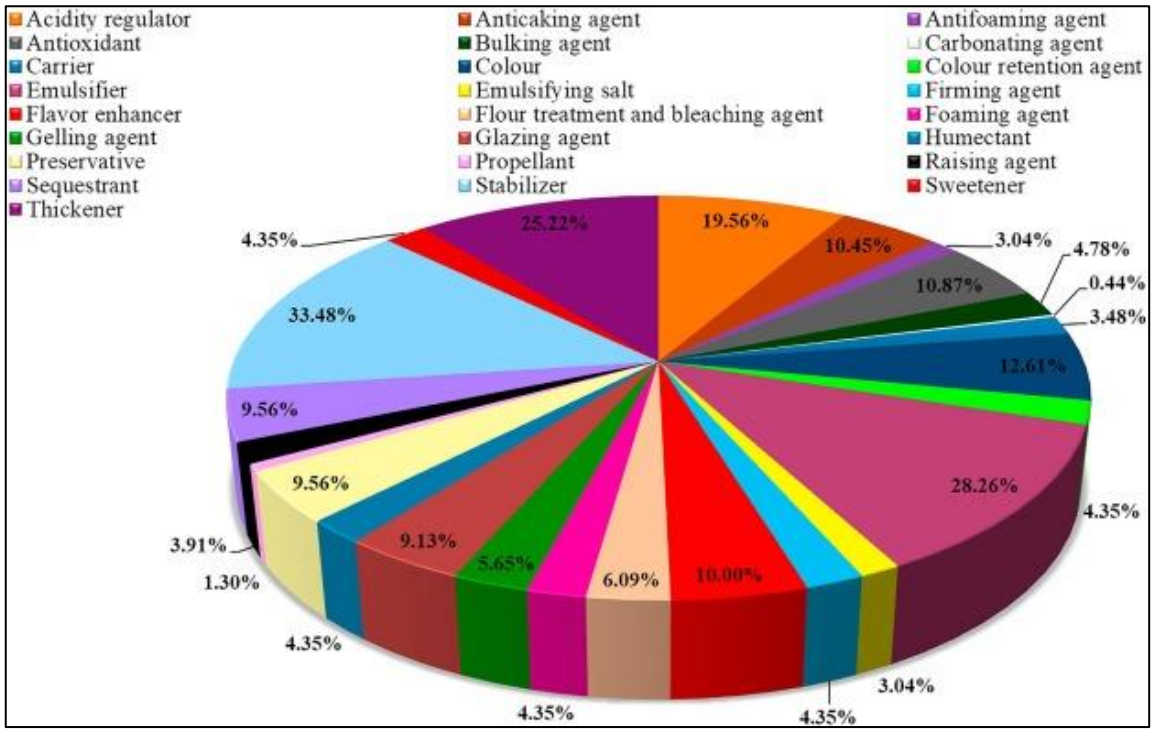


Fig. 32 several types of the food additives used in food industries (Martins et al., 2018).

Dietary emulsifiers, such as carboxyl methyl cellulose (CMC) and polysorbate-80 (P80), are associated with gut microbiota alteration and impairing intestinal barrier function. Emulsifier consumption reduces gut microbial diversity, increasing Verrumicrobia (*Akkermansia muciniphila*) and Proteobacteria, while decreasing Bacteroides abundance. Dysbiosis resulted from these microbiota changes, increases bacterial translocation across intestinal epithelium, thus potentially increasing the incidence of inflammatory bowel disease, weight gain, and metabolic syndrome **(Ishiguro et al., 2018; Zhang et al., 2018**, **Rinninella et al., 2019)**.

In addition to dietary emulsifiers, non-caloric artificial sweeteners (NASs)_also known as non-nutritive sweeteners (NNS)_ such as potassium, aspartame, saccharin, sucralose, and neotame, are introduced as means for providing sweet taste to foods without the associated high energy content of caloric sugars (**Ishiguro et al., 2018, Lu and Zuo, 2018).** NAS consumption alters the composition and function of the gut microbiota, increasing the abundances of Firmicutes, Bacteroidetes and Lactobacilli spp **(Liauchonak et al 2019; Wu et al., 2019).**

Studies demonstrate that NAS-induced changes in gut microbiota composition modify microbial metabolic pathways, and that these changes are linked to

dysbiosis, and metabolic abnormalities that might enhance the risk of glucose intolerance **(Lu and Zuo, 2018; Zhang et al., 2018; Rinninella et al., 2019).** Whereas others have found associations between NAS intake and weight gain, higher risk of type 2 diabetes, and insulin resistance **(Fig 33) (Zhang t al., 2018; Liauchonak et al 2019).**

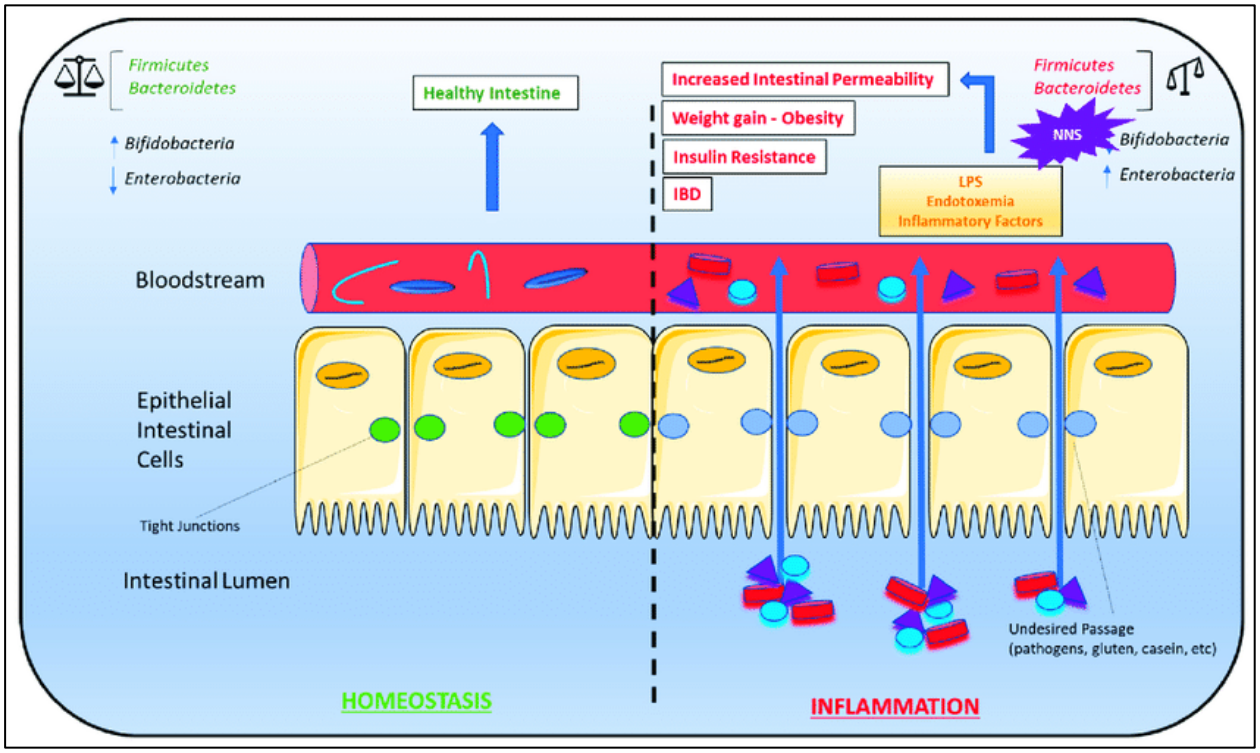


Fig. 33 the impact of NNS (non-nutritive sweeteners) on gut microbiota and health outcomes (Liauchonak et al., 2019).

4. Dietary patterns

According to the Office of Disease Prevention and Health Promotion, the definition of dietary patterns is "the quantities, proportions, variety or combinations of different foods and beverages in diets, and the frequency with which they are habitually consumed", so instead of focusing on specific nutrients or foods, diet pattern analysis examines the effects of a person's total diet as a whole **(Del Chierico et al., 2014; Ishiguro et al., 2018).**

Changes in diet, even within a short duration, has a significant impact on the composition of the gut microbiota, which in turn determines functional gene expression and metabolic production. In healthy people, a well-balanced diet can

help to create a good microbial flora, in which all types of bacteria coexist in harmony. An unbalanced diet, on the other hand, might cause gut bacteria dysbiosis, which can lead to diseases **(Fig. 34) (Tan and O'Toole, 2015; Sandhu et al., 2017; Garcia-Mantrana et al.,2018; Merra et al., 2021).**

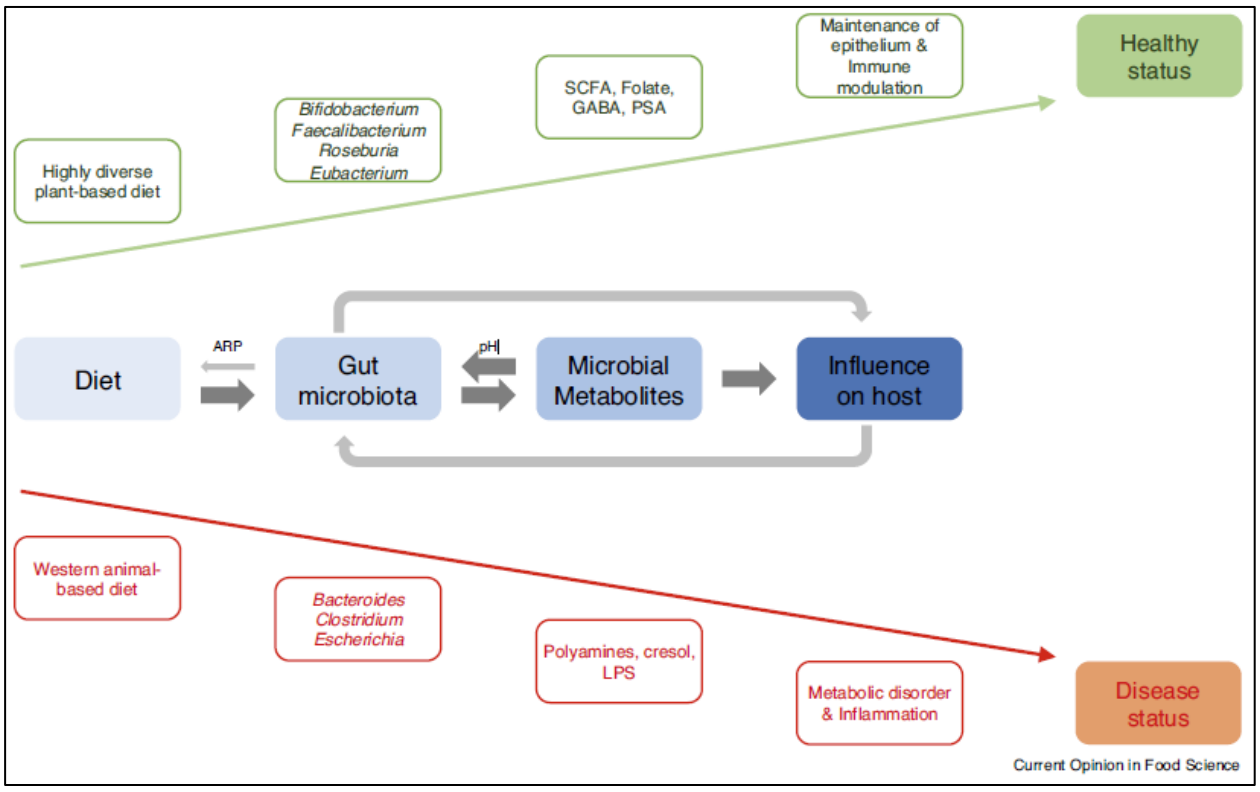


Fig. 34 Interactions between diet, gut microbiota, microbial metabolites and host. ARP: appetite-regulating peptides; SCFA: short chain fatty acid; GABA: g-Aminobutyric acid; PSA: polysaccharide A; LPS: lipopolysaccharide (Tan and O'Toole, 2015).

Western, gluten-free, omnivore, vegetarian, vegan, and Mediterranean diets all have various effects on the composition of the gut microbiota and an individual's overall physiology **(Table 4) (Sandhu et al., 2017; Singh et al., 2017)**. Herein, we'll look at three different diets: Western, Vegetarian, and Mediterranean, all of which have different effects on the gut microbiota of the person who consumes them.

Table 4. Effects of special diets on gut microbiota (Singh et al., 2017).

Diet	Food constituents	Total bacteria	*Bifidobacteria*	*Lactobacilli*	*Prevotella*	*Eubacteria*	*Roseburia*	*Bacteroides*	*Enterobacteria*
Western	High animal fat/protein	↓	↓	↓		↓		↑	↑
Mediterranean	High fiber/antioxidants/UFA low red meat	↑	↑	↑	↑	↑	↑	↑	
Gluten-free	No gluten	↓	↓	↓	↓	↓	↓		↑

UFA unsaturated fatty acids

4. 1. Western diet

Following the industrial revolution, dramatic lifestyle changes occurred, including a nutritional shift from a traditional diet to a Western one (WD) **(Daïen et al., 2017)**. WD is a dietary habit adopted by many people in developed countries as part of their Western lifestyle. When compared to the diet of those living in rural areas, which is enriched with fiber and complex sugars, the WD provides a high amount of fat, animal proteins, and refined carbohydrates with lower quantity of fiber **(Fig. 35) (Graf et al., 2015; Makki et al., 2018; Rinninella et al., 2019).** Moreover, this diet contains high concentrations of ultra-processed foods and potentially harmful dietary additives such as emulsifiers and artificial sweeteners **(Fig. 35)**, as well as a macronutrient imbalance and micronutrient deficiency **(Daïen et al., 2017; Ramos and Martín, 2020).**

The Western diet pattern is thought to promote pro-inflammatory cytokines, alter intestinal permeability, and influence the gut microbiota **(Fig. 35)**, increasing the risk of gastrointestinal disorders such as large bowel cancer, gall stones, and Crohn's disease **(Moco and Ross, 2014; Ishiguro et al., 2018).**

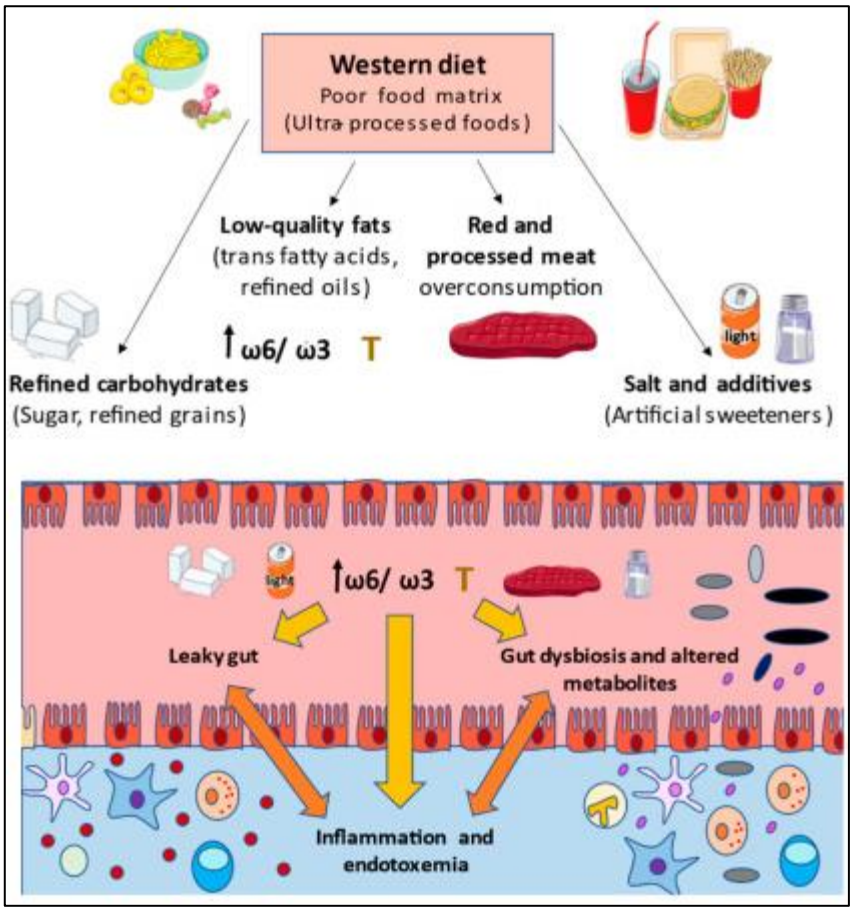


Fig. 35 the composition and effects of western diet pattern (García-Montero et al., 2021).

WD Consumption contributes to negative changes in microbiota composition and may result in progressive decreases in gut microbial diversity that cannot be entirely regained by reintroducing traditional diets **(Shen, 2017; Azcarate-Peril et al., 2019; Ramos and Martín, 2020).** According to multiple studies, a Western diet reduced the number of total bacteria and beneficial Bifidobacterium and Eubacterium species, as well as the amount of Bacteroidetes, while increasing the number of Proteobacteri and Firmicutes **(Fig. 36) (Singh et al., 2017; Senghor et al., 2018; Ramos and Martín, 2020).** Whereas, Other studies found that a diet high in animal protein and fat, which is common in western societies, favors the abundance of bile-tolerant microorganisms like Alistipes, Bilophila, and Bacteroides and decreases the levels of Firmicutes, while Prevotella enterotype was underrepresented in the WD microbiota and predominates among people who consume more fiber **(Fig. 36) (Coelho, et al., 2018; Rinninella et al., 2019).**

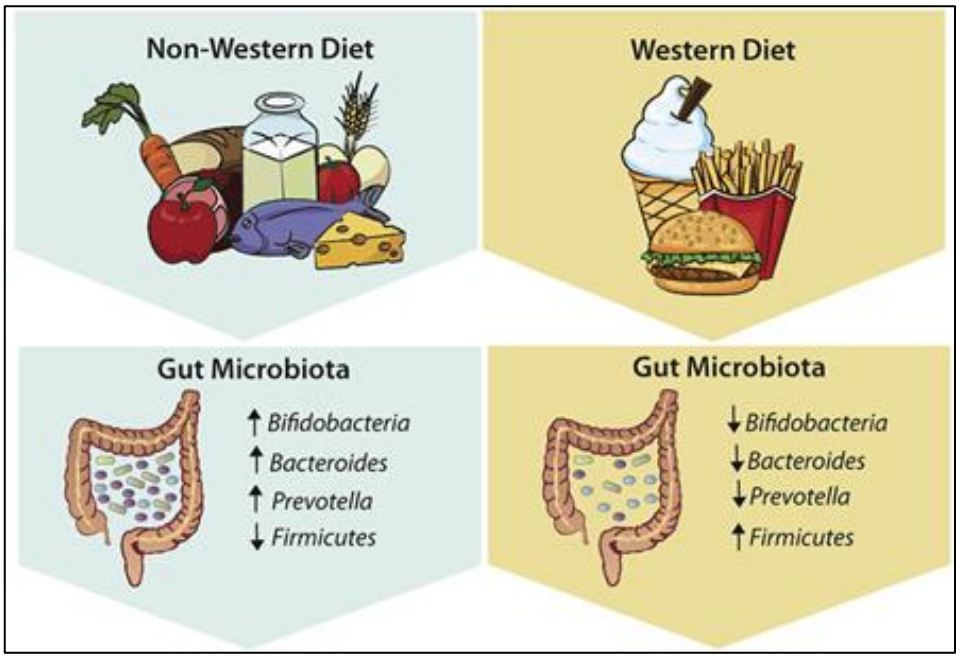


Fig. 36 The impact of A nonwestern vs a Western diet on gut microbiota composition (Sandhu et al., 2017).

4. 2. Vegetarian diet

A vegetarian dietary pattern contains a high intake of fruits, vegetables, fiber, whole grains, nuts, soy products, and phytochemicals (carotenoids and polyphenols) **(Fig. 37)**, as well as a low intake of saturated fat, sodium, and high-calorie meals **(Yeh et al., 2016; Sakkas et al., 2020).** While vegetarians exclude all sorts of meat and seafood from their diet, vegans avoid eating animal products also such as eggs, honey, milk, and dairy products **(Rinninella et al., 2019).**

When compared to nonvegetarians, vegan/vegetarian diets are associated with better health outcomes and lower disease risk, including cardiovascular disease, hypertension, diabetes, obesity, cancer, renal illness, diverticulitis, gall stones, and rheumatoid arthritis (RA). The source of these health benefits appears to be the increased polyphenol and fiber consumption combined with a reduction in meat and/or animal products. **(Yeh et al., 2016; Gentile and Weir, 2018, Ishiguro et al., 2018).**

The microbiota of a vegetarian population is compared to those of omnivores to determine the direct association between this diet and alterations in the gut microbiome. In this regard, it has been shown that vegetarian/vegan diets promote

distinct microbiota than omnivore diets, with just a slight variation between vegans and vegetarians **(Do Rosario et al., 2016; Tomova et al., 2019).** Indeed, studies have shown that omnivores' microbiota is enriched with butyrate-producing *Clostridium cluster XIVa* bacteria, whereas vegetarians and vegans had higher ratios of Bacteroides/Prevotella, *Bacteroides thetaiotaomicron, Clostridium clostridioforme, Klebsiella pneumoniae,* and *Faecalibacterium prausnitzii* and lower ratios of *Clostridium cluster XIVa and Bilophila wadsworthia* **(Graf et al., 2015; Rinninella et al., 2019).**

Other variations in the relative abundance of numerous taxa were observed among vegetarians, including a decrease in *Collinsella, Holdemania, Clostridium perfringens* and *Clostridium histolyticum* due to polyphenols as well as an increase in *Roseburia, Lachnospiraceae, Prevotella, Bifidobacterium*, and *Lactobacillus* **(Fig. 37) (Barrett et al., 2018; Sakkas et al., 2020).**

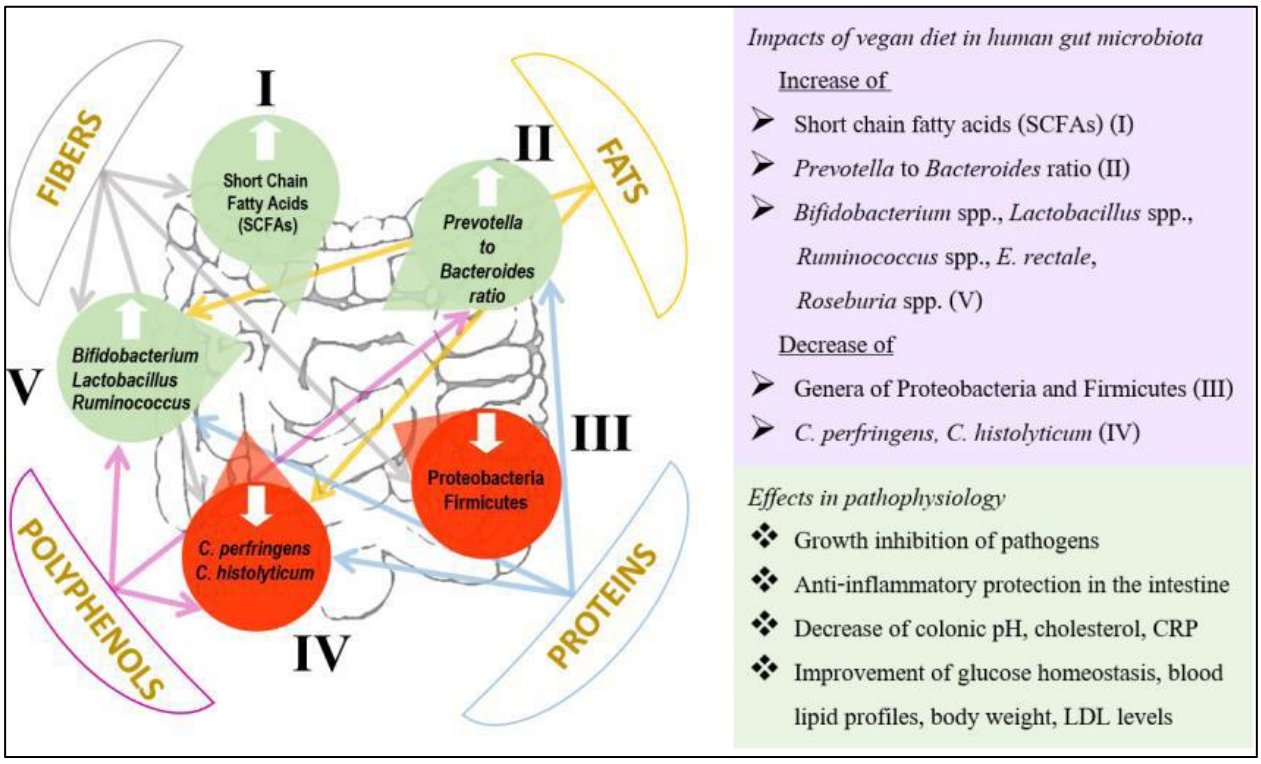


Fig. 37 Impact of vegan food components in the human gut microbiota. *E. rectale: Eubacterium rectale; C. perfringens: Clostridium perfringens; C. histolyticum: Clostridium histolyticum.* LDL: low-density lipoprotein; CRP: C-reactive protein **(Sakkas et al., 2020).**

4. 3. Mediterranean diet

The Mediterranean diet (MedDiet or MD) is a dietary pattern that consists mainly of vegetables, legumes, fruits, nuts, and olive oil, with moderate consumption of fish, poultry, dairy products, and alcohol (mainly wine during meals) and low consumption of red meat, processed meat, and sweets. In addition, MedDiet includes physical activity on a daily basis to maintain a healthy physical state **(Fig. 38) (Sandhu et al., 2017; Ishiguro et al., 2018; Ghosh et al., 2020).** Mediterranean diets are nutritionally balanced dietary pattern, it is high in carbohydrates, proteins, and fibers, and low in fats. Fiber and chemical components such as flavonoids, phytosterols, vitamins, terpenes, and phenols are found in vegetables, fruits, and nuts, while olive oil is the most commonly consumed fat **(Del Chierico et al., 2014; Calabrese et al., 2021)**.

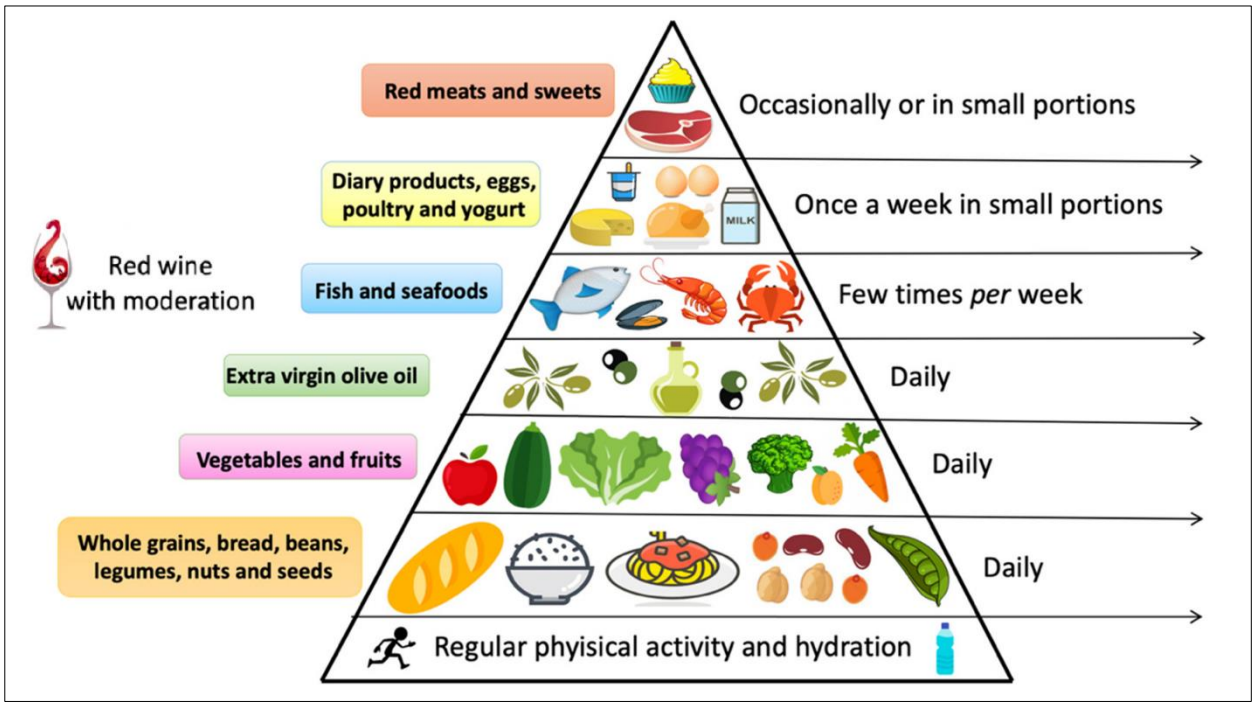


Fig. 38 Pyramidal representation of Mediterranean dietary patterns (MDPs) and the frequency of recommended intake (Merra et al., 2021).

This dietary pattern was linked to considerable benefits in health, including a lower risk of type 2 diabetes, obesity, cancer, Alzheimer's disease, metabolic syndrome, inflammatory disorders, and cardiovascular illnesses **(Fig. 39) (Ishiguro et al., 2018; Nagpal et al., 2019).** MD's therapeutic advantages are linked to its

potential to alter the composition of the gut microbiota, resulting in the creation of a number of metabolites that support metabolic and molecular health **(Calabrese et al., 2021)**. The gut microbiota of obese people, for example, has been shown to change due to MDP, with an increase in Bacteroides, Prevotella, and, most importantly, *Roseburia*, *Ruminococcus*, *Parabacteroides distasonis*, and *Faecalibacterium prausnitzii*, bacteria known for their saccharolytic activity and ability to digest carbohydrates **(Nagpal et al., 2019; Vernocchi et al., 2020)**.

At phylum level **(Fig. 39),** Mitsou et al. **(2017)** confirmed the positive impact of the MD on the gut microbiota profile. In fact, subjects who had a higher adherence to the MD, had a lower presence of *E. coli* and a higher culture-based *Bifidobacteria/E. coli* ratio; moreover, increased levels of *Candida albicans*, *Faecalibacterium prausnitzii*, *Clostridium cluster*, and SCFAs, were also reported due to MedDiet intake **(Calabrese et al., 2021)**.These positive effects are believed to be derived from Mediterranean diet's high carbohydrate, fiber, unsaturated lipid, and antioxidant content, as previously documented **(Mitsou et al., 2017; Ishiguro et al., 2018)**.

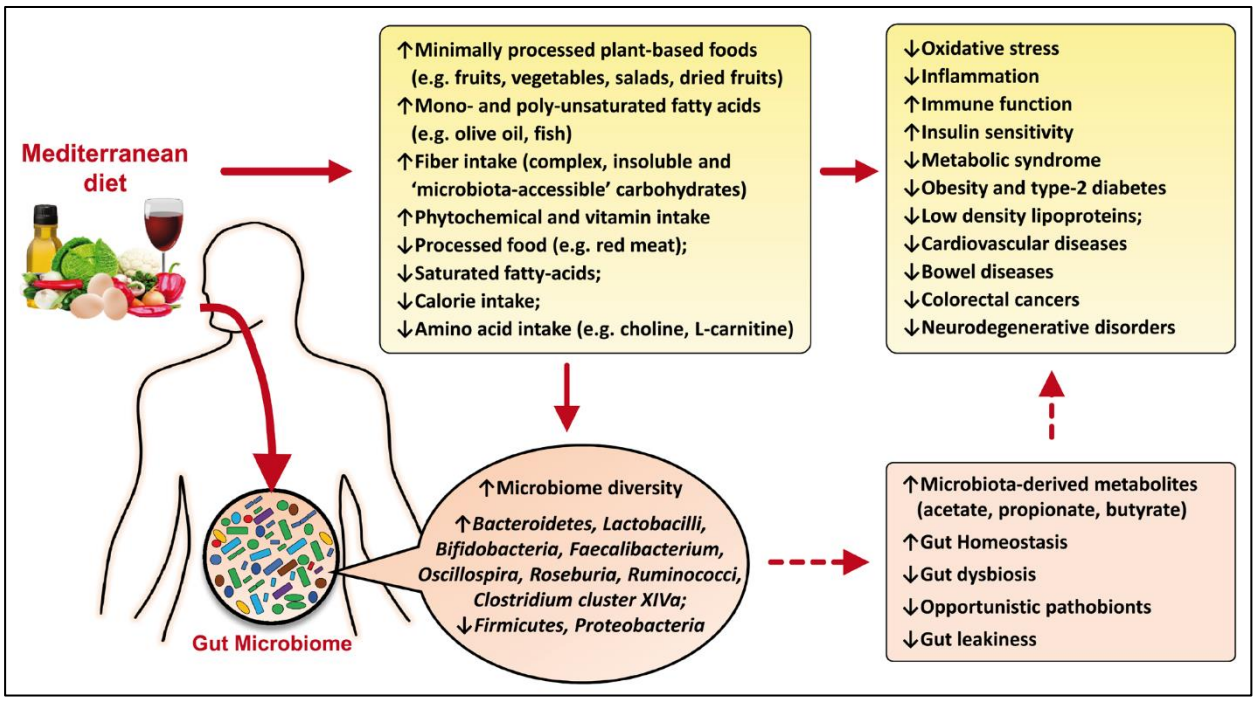


Fig. 39 Correlation between Mediterranean diet and intestinal bacterial growth (Nagpal et al., 2019).

Fig. 40 summarize the effects of diets patterns discussed above and others on commensal bacterial species.

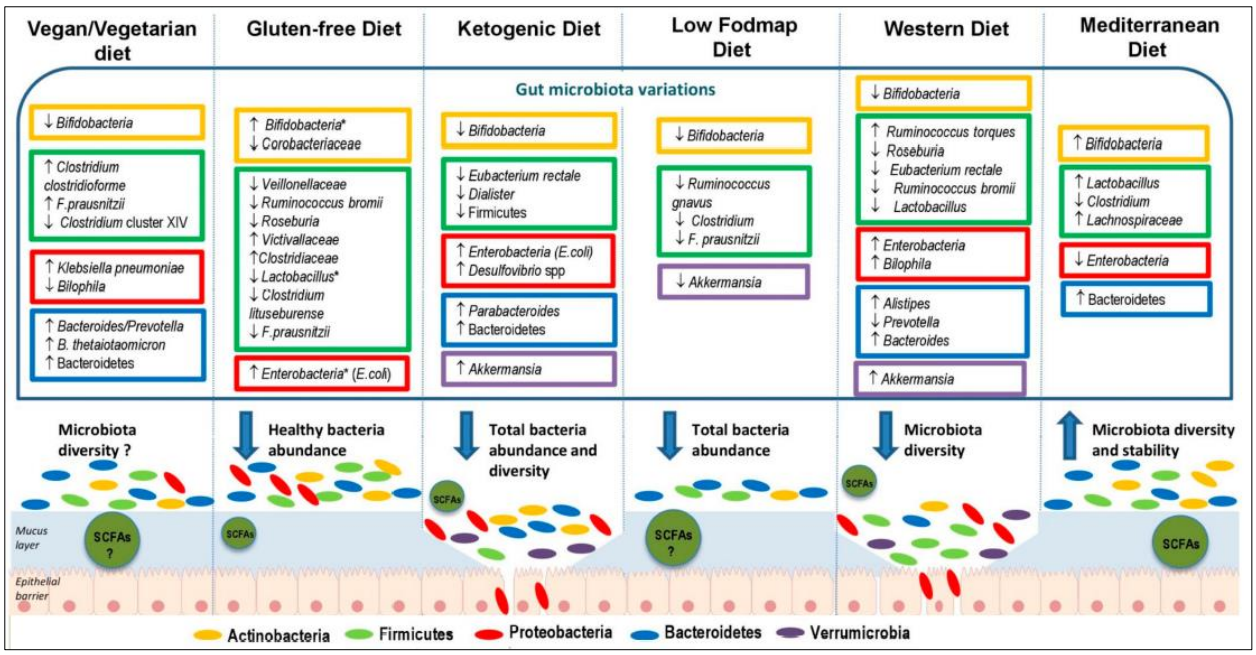


Fig. 40 Effects of different types of diet on gut microbiota (Rinninella et al., 2019).

Chapter three: Impact of food altering gut microbiota

Chapter three: Impact of food altering gut microbiota

Diet and microbial metabolites derived have serious implications for the development of several diseases specially the food associated ones. However, additional researches need to be carried out to determine risk indicators for these diseases associated with microbiome. In turn, healthy diets and particular nutritional measures such as the increase of dietary fiber and the use of probiotics and prebiotics might serve to restore the beneficial bacteria and variety of microbiota, which may move from disease to health-promoting states **(Requena et al., 2018; sing et al., 2017).**

1. Role of the gut microbiota in health and disease

Many of the bacteria that stably inhabit the human gut create a mutually beneficial connection with the host **(Manor et al., 2020)**. The total of all the symbiosis between host and microbiota in the community and among various microbial species leads to eubiosis, an equilibrium that is crucial to the maintenance of intestinal, immunological, and metabolic homeostasis. Dysbiosis is the opposite of eubiosis, and is characterized by qualitative and quantitative changes in composition, geographic distribution and the function of the microbial symbiotic community**.** In fact, dysbiose has been indicated as crucial in terms of intestinal pathologies and it disrupts not only the intestine but also other, much further organ systems **(Kovatcheva-Datchary et al., 2013; Guinane and cotter, 2013).**

In this section we have discussed some of the various ways in which alterations in the microbiota are linked to diseased states, commonly referred to as dysbiosis. Moreover, in the majority of cases, the link between dysbiosis and disease etiology is unknown at this moment and it is frequently not obvious whether microbiome alterations related to diseases are significant and whether they are a cause or an effect. And as we understand more about how the microbiota influences the host we observe that dysbiosis may cause disease, but it’s also worth noting that the disease condition can alter the microbiota through a variety of methods, including changes

in dietary habits and intestinal function, as well as the use of antibiotics **(Shreiner et al 2015).**

Many human gastrointestinal disorders (inflammatory bowel diseases, irritable bowel syndrome) as well as other diseases including, diabetes, obesity, cancer, cardiovascular and central nervous system disorders are linked to dietary changes, and several of these are linked to changes in the gut flora. However, for the majority of these diseases, researches are still developing to find out the direct relationship between food, the gut microbiome and diseases development **(Fig. 41) (Albenberg et al., 2014; Silvestre et al., 2018).**

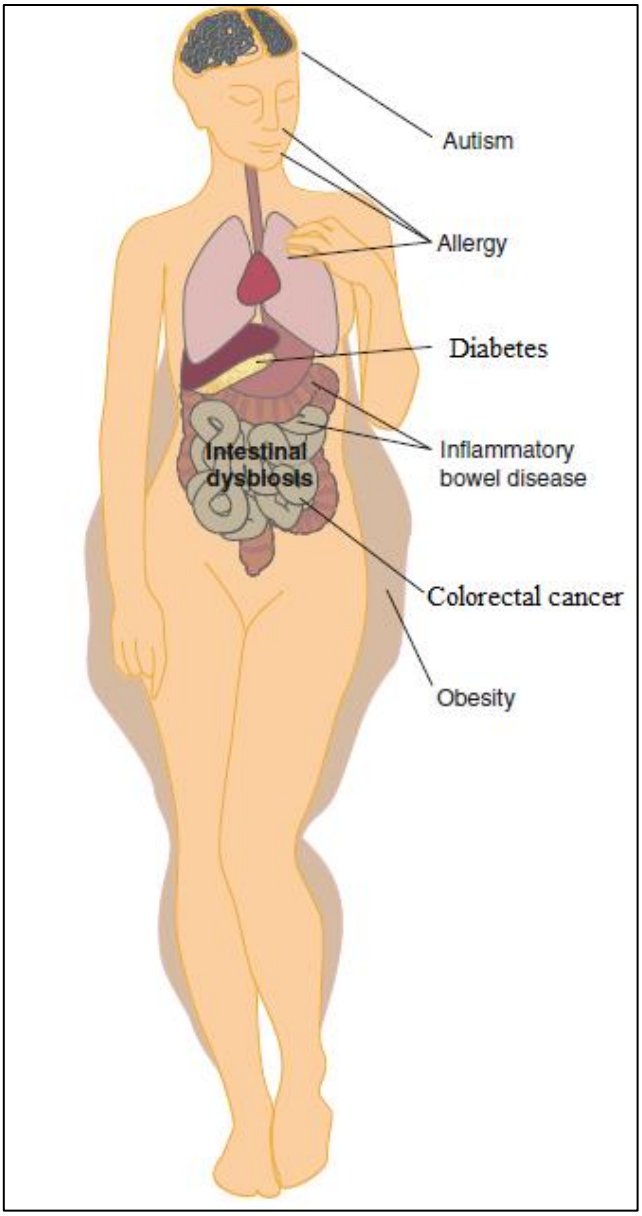


Fig. 41 Some Gut microbiota-related diseases (Kovatcheva-Datchary et al., 2013)

Here are a few of the current results on the involvement of bacteria in particular diseases including inflammatory bowel diseases, colorectal cancer, and diabetes.

1. 1. Inflammatory bowel disease (IBD)

IBD is a chronic and relapsing intestinal inflammation disorder that is divided into two clinical phenotypes: ulcerative colitis (UC) and Crohn's disease (CD). Mucosal inflammation in the colon is what UC is characterized by, it has a continuous and circumferential pattern of inflammation that begins in the rectum and extends proximally. CD, on the other hand, can affect any portion of the GI tract with localized and transmural lesions. Both types of IBD are characterized by persistent relapses that can be treated medically, but in severe cases, surgery may be necessary **(Matsuoka and Takanori, 2015; Miyoshi et al., 2016).**

Apart from traditional pathogens, the gut microbiota can promote pathogenicity through one of two mechanisms: an increase in pro-inflammatory species or a decrease in the microbiome's defensive chemicals. Because of the microbiota's complexity, both pathways are observed in patients with IBD when compared to healthy individuals. The most constant alterations include a decrease in the gut microbiota diversity and a decrease in Firmicutes abundance. There have been also reports of increases in the abundance of Proteobacteria and Bacteroidetes, as well as declines **(Nishida 2017; seksik, 2010).** However, it's unclear if the dysbiosis seen in IBD is a cause or a result of the inflammation in the intestine **(Matsuoka and Takanori, 2015).**

The gut microbiome appears to differ between UC and CD. In fact, as compared to controls, UC patients had lower levels of the butyrate-producing bacteria *Roseburia hominis* and *Faecalibacterium prausnitzii* **(Machiels et al., 2014).**

In CD patients, on the other hand, higher *Faecalibacterium prausnitzii* levels, as well as a reduction in total diversity, have been found. Another research reported a reduction in *Dialisterinvisus* (an unidentified Clostridium spp. Species), *Faecalibacterium prausnitzii*, and *Bifidobacterium adolescentis*, as well as an increase in *Ruminococcus gnavus* in CD patients **(Joossens et al., 2011).**

Furthermore, other research showed that taking live *Faecalibacterium prausnitzii* by mouth decreased the severity of colitis and helped to rectify the dysbiosis. These findings indicate that employing *Faecalibacterium prausnitzii* as a probiotic to treat dysbiosis is a potential CD therapy option **(Rinninela et al, 2018).**

The pathophysiology of IBD is also linked to the synthesis of metabolites influenced by gut microbiota disturbance. SCFA levels have been shown to drop in IBD patients as a consequence of butyrate-producing bacteria such *F. prausnizzi* and *Clostridium clusters IV, XIVa,* and *XVIII* **(Takahashi et al., 2016).**

Reduced SCFA synthesis impacts Treg cells (T regulatory cells) differentiation and expansion, as well as epithelial cell proliferation, all of which are critical for maintaining intestinal homeostasis. However, In IBD patients the quantity of sulfate-reducing bacteria, such as *Desulfovibrio*, is increased, leading in hydrogen-sulfate formation, which destroys intestinal epithelial cells and causes mucosal inflammation. These findings clearly suggest that changes in the gut microbiota are linked to the pathophysiology of IBD **(Fig. 42) (Nishida 2017).**

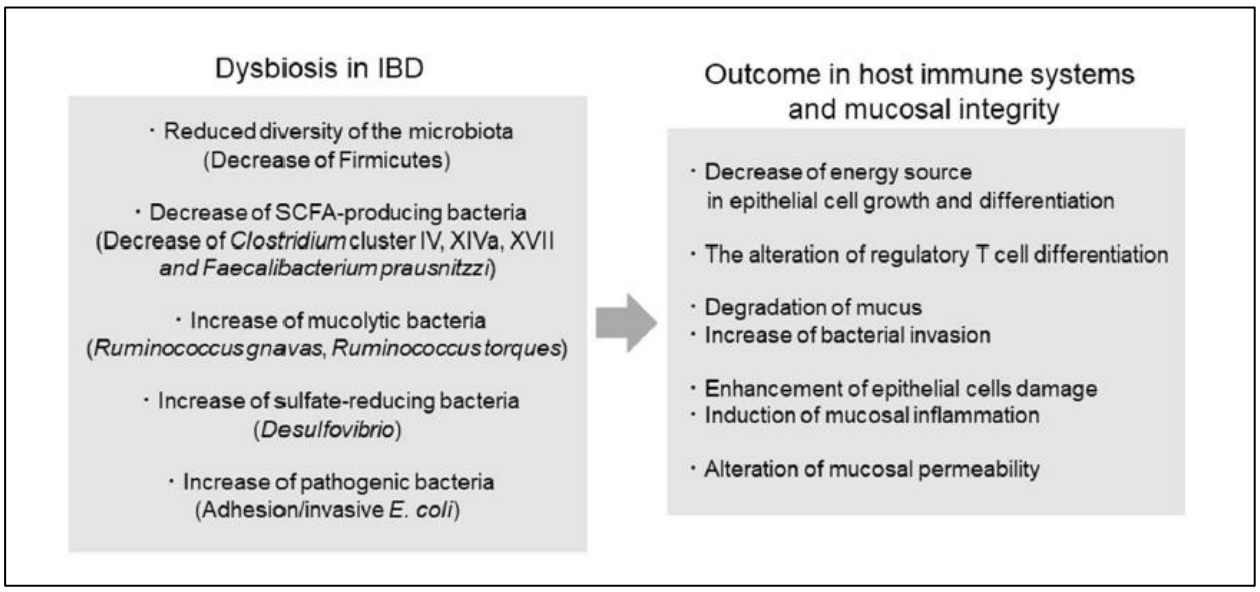


Fig. 42 IBD dysbiosis and dysbiosis pathological results (Nishida 2017).

Because nutrition may affect the structure and function of the intestinal microbiome, it's plausible to believe that diet is implicated in the pathogenesis of IBD and might possibly be a therapeutic target **(Albenberg et al., 2014).** In addition

to its interactions with microbiome that certainly plays an important role in disease onset **(Dolan and Chang, 2017).**

Several researches have looked at the link between dietary habits and the occurrence of IBD. According to a systematic review, diets high in total fats, polyunsaturated fatty acids, omega-6 fatty acids, meat, and food additives such as sweeteners, emulsifiers, and preservatives may alter the host-microbiota interaction, which leads to a microbiota that encourages inflammation of the intestines and increases the mucolytic activity and are linked to an increased risk of CD and UC, high fiber and fruit intake are linked to a lower risk of CD, while high vegetable intake is linked to a lower risk of UC **(Albenberg et al., 2014; Requena et al., 2018; Chassaing et al., 2015).**

The ingestion of indigestible and poorly absorbed short-chain carbohydrates has also been linked to the onset of symptoms in IBD patients. In contrast, a diet high in fish, as well as fermentable fibers, fruits and vegetables lowers the risk of IBD. Furthermore, dietary vitamin and mineral deficiency is likely to have a role in the pathogenesis of IBD **(Requena et al., 2018).**

1. 2. Cancer

Cancer is a complex disease that is the world's second biggest cause of mortality. Recently, several researches have highlighted the gut microbiota's dual function in defending the host's health with many metabolites and biological products that are produced by intestine resident bacteria to protect the host and maintain intestinal homeostasis. During pathogenic dysbiosis, on the other hand, numerous microbiota subpopulations may increase and create excessive quantities of toxins, which can cause inflammation and cancer **(Vivarelli et al., 2019; Xavier et al., 2020).**

The microbiome has been linked to carcinogenesis in both direct and indirect ways. Pathogens colonizing epithelia or interacting directly with the innate immune system are examples of direct routes. Bacterial creation of carcinogens and chemoprotective factors from exogenous sources, such as diet, or endogenous sources, such as compounds produced by human metabolism for example bile acids

and steroid hormones, are examples of indirect routes **(Hullar et al., 2014; Rooks and Garrett, 2011; Lampe JW (2008).**

Carcinogenesis can be generated by certain gut microbiomes and their dysbiosis in several ways, including direct DNA damage and inflammation, indirect immune response regulation, and chronic inflammatory responses caused by bacterial metabolites **(Rajagopala et al., 2017)**. The metabolic imbalance and increased generation of carcinogens associated with microbial dysbiosis cause direct DNA damage. While certain microbial families provide cancer therapy resistance, others are required for some therapies to be totally effective **(Fig. 43) (Halley et al., 2020).**

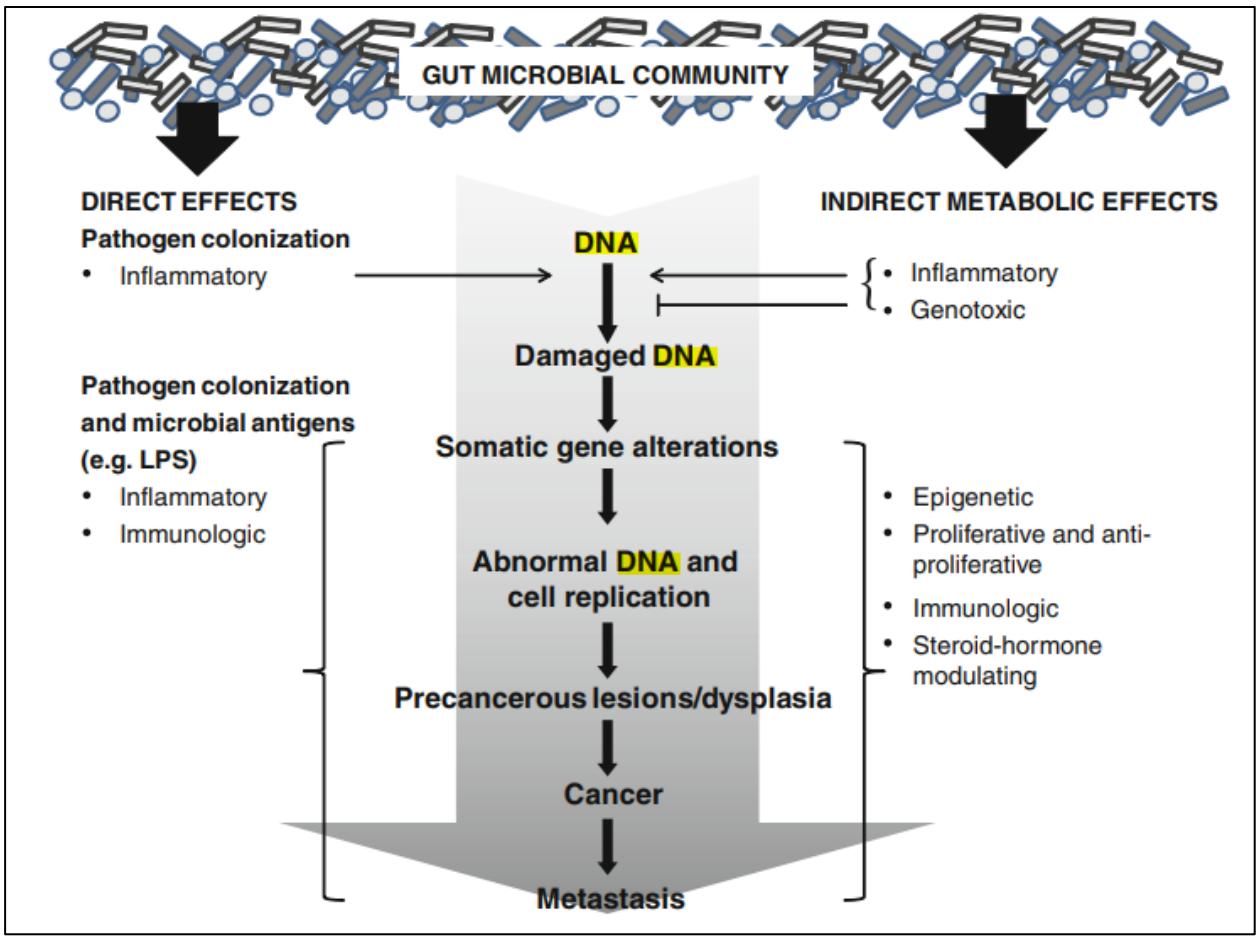


Fig. 43 Direct and indirect processes that may affect the gut microbial ecosystem on the risk of cancer (lipopolysaccharide=LPS) **(Hullar et al., 2014).**

Also, many intestinal microorganisms, known as probiotics, have been linked to the prevention of tumor formation. Probiotics have been tested to help battle

dysbiosis in cancer patients undergoing chemotherapy and radiation due to their capacity to preserve gut homeostasis **(Vivarelli et al., 2019).**

1. 2. 1. Colorectal cancer (CRC)

Colorectal cancer (CRC) is one of the most frequent malignancies worldwide, with a significant global health impact. Tumor formation in the large bowel is complex, as is the case with many diseases, and a variety of hereditary and environmental variables play a role in disease progression **(Wong et al., 2019).**

It was demonstrated that the microbial diversity in the tumor tissue was much lower than that in the tissue of noncancer, Lactobacillales were increased in cancer tissues, while Faecalibacterium was decreased. In addition, there were considerable differences in the microbial structure of the intestinal lumen and tissue **(Chen et al., 2012)**. In addition to that, Bifidobacterium, Faecalibacterium, and Blautia were shown to be decreased among the mucosa-adherent bacteria of CRC patients. On the other hand, Fusobacterium and Phorphyromonas were increased **(Requena et al., 2018;Castellarin *et al.* 2012).**

The Fusobacterium genus, which includes *Fusobacterium nucleatum, Fusobacterium mortiferum, and Fusobacterium necrophorum* sequences, were found to be abundant in tumor tissue in the study of the colorectal microbiome. These alterations were followed by wide phylum-level changes, including a large decrease in Firmicutes and Bacteroidetes. This might indicate that *Fusobacterium spp*. has a role in tumorigenesis via an inflammatory mechanism **(Kostic *et al.* 2012; Guinane and Cotter, 2013).**

A number of additional researches have also pointed the relationship between microbially caused inflammation and CRC. Microbial compounds have been shown to enter barrier-defective colonic tumors, activate inflammation through a host immunological response, and as a result, accelerate tumor development **(Grivennikov *et al.* 2012; Guinane and Cotter, 2013).**

The risk of Colon cancer also depends on the balance among microbial production of health-promoting metabolites such as butyrates and potentially

cancerous metabolites such secondary bile acids. Butyrate is a chemoprotective agent that can reduce proliferation and increase apoptosis in CRC cells. However, butyrate can also reduce carcinogenesis by reducing inflammation and colonocyte permeability while preserving epithelial barrier function **(Ou et al., 2013).**

Inflammation is another crucial relationship between the intestinal microbiota and the CRC. A recent study has shown a distinct correlation between bacterial clusters associated with the CRC and profiles of the mucosal genes for immunoinflammatory responses **(Requena et al., 2018).**

Diet, eating habits and colorectal cancer (CRC) are significantly associated. On the one hand, epidemiological trials have shown that fruit, vegetables and whole grain diet reduced risk of CRC. On the other hand, the intake of red and processed meat as well as animal feed typical of the western diet is today clearly shown to raise the CRC risk. Recent research has shown that the relations of meat intake with CRC vary by the kind of food, sex and tumor location in the intestines **(Vulcan et al., 2017).**

1. 3. Diabetes

Diabetes mellitus (DM) also called diabetes is a metabolic disease that affects several organs and it represents a growing problem that currently affects 1 in 11 adults worldwide. With several types including Type 1 diabetes (T1D), an autoimmune disease caused by the destruction of the pancreatic islets' insulin-producing b cells by T lymphocytes **(Kostic et al., 2015)** and Type 2 diabetes (T2D) which represents a significant risk factor for heart disease and stroke, and it has risen to the top of the global illness burden **(Li et al., 2020).**

According to a recent research, people with diabetes attend to have an intestinal dysbiosis **(Das al., 2021)** and it has been revealed that T1D and T2D are linked to several variables including gut microbiota changes **(Li et al., 2020).** In addition to what have been discovered among different processes including production of low-grade inflammation, energy homoeostasis, and glucose metabolism that showed the ability of the gut microbiota to interact with host metabolism leading to insulin

resistance and T2D **(Allin et al., 2015).**

The gut microbiota composition appeared to be different between healthy persons and diabetics, with T2D patients having much less *Clostridium cluster IV* and *subcluster XIVa* components and considerably more Lactobacillales and Bifidobacterium populations. But in T1D, the Bacteroidetes-to-Firmicutes ratio grew throughout time, whereas it decreased in nondiabetic individuals. Another evidence for the importance of microbiota in T1D pathogenesis is the lower frequency of the genera Faecalibacterium and Prevotella in diabetics, while the Bacteroides was somewhat more abundant in diabetics than in healthy patients **(Grigorescu and Dumitrascu, 2016; Gurung et al., 2020).**

On the contrary of that, a 2021 research has revealed that the abundance of the predominant Phyla in humans' gut (Firmicutes, bacteroidets, protectobacteria and actinobacteria) was not significantly different between diabetics and healthy persons. So for the first time it has been demonstrated that *E. coli* that produced amyloid, their phages as well as bacteria-derived amyloid may be implicated in pro-diabetic pathway activation in children at risk for T1D **(Das et al., 2021).**

According to new research, adults with T2D have a different gut microbiome than healthy persons. Although the question of whether these alterations are a cause or an effect is still debated in many cases **(Guinane and Cotter, 2013).**

On the other hand, Diet appeared to have a bigger impact on diabetes development than microorganisms, and the gut inflammation caused by it may be a precondition for gut pathogen–induced islet autoimmunity. Dietary management would be the primary non-pharmacologic strategy for preventing T2D, since it would restore the balance of the gut bacteria and, as a result, the metabolic processes **(Grigorescu and Dumitrascu, 2016).**

Dietary changes are a key contributor to the rise in diabetes. Consuming more processed carbs while consuming less dietary fiber (DF) has been identified as a key risk factor for diabetes **(Kim, 2017).**

The human host diet offers nondigestible carbohydrates to promote bacterial

development, and in return, the bacteria produce SCFAs, which serve as an energy source for colonocytes, reduce inflammation, and control satiety, among other things. SCFA deficiency has been linked to a variety of illnesses, including type 2 diabetes (T2D) **(Zhao et al., 2018).**

Through the generation of SCFAs, the gut microbiota has an impact on glucose and energy metabolism. The colonic gut bacteria produce butyrate, acetate, and propionate, which enter the bloodstream after fermentation of complex polysaccharides **(Kim, 2017).**

Butyrate and propionate, for example, have recently been discovered to trigger intestinal gluconeogenesis via complimentary pathways. As a result, SCFAs may have an impact on host glucose metabolism through regulating intestine gluconeogenesis. While Acetate reaches the brain and decreases appetite to decrease food consumption. These findings suggest that SCFAs have pleiotropic and mostly positive impacts on host metabolism, as well as new targets for type 2 diabetes therapies and prevention **(Fig. 44) (Allin et al., 2015; kim, 2017).**

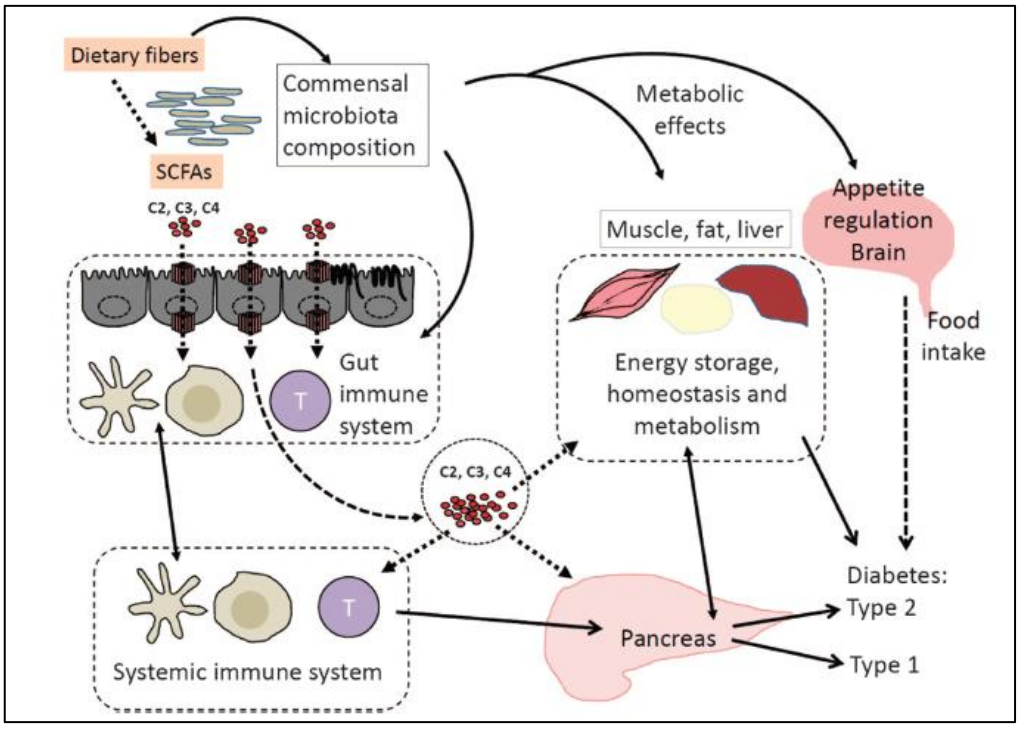


Fig. 44 DF and SCFAs beneficial effects on diabetes (C1= Acetate, C2= Propionate, C3= Butyrate) (kim, 2017).

Endotoxins produced by gram-negative bacteria in the gut could be one of the causes/mediators of low-grade systemic inflammation; their circulation is impacted by dietary changes, particularly in T2D patients **(Grigorescu and Dumitrascu, 2016).**

Therapeutically speaking, the gut immune system should be included in the targets for any intervention to prevent or cure patients with T1D. While to prevent T2D, Constant microbial stimulation, restricted diets and the use of probiotics and prebiotics would be the key for non-pharmacologic solution **(Alokail et al., 2013).**

Despite multiple studies showing the function of intestinal microbiota in T2D pathogenesis, the studies continue to evolve. Today, we think that several microbial taxa and related molecular pathways are involved in the metabolism of T2D glucose. We must, on the other hand, aim for precise/personalized therapy that prescribes anti-diabetics and probiotics for a single patient based on the combination of its mammalians and microbes' genomes **(Gurung et al., 2020).**

2. Association between food, gut microbiota and diseases

There is a considerable amount of data suggesting the importance of food in creating the composition and metabolome of the human gut microbiome, with research revealing that dietary changes may induce major, temporary microbial shifts within 24 hours **(Singh et al., 2017).** Functional research in animal models, along with descriptive association studies in humans, offers evidence for the importance of food in disease etiology through its impact on intestinal microbes **(Albenberg et al., 2014; Zmora et al., 2019).**

As it was presented, previously, in the present work microbes that live in the human intestinal tract depends on their hosts for fermentable substrate and use it to create a wide range of diet-derived and secondary metabolites by metabolizing the end-products of human digestion and indigestible food substrates. These microorganisms and their metabolites tend to influence the immunological and neurological systems through known and undiscovered pathways, impacting human

physiology and disease progression **(Gentile and Weir, 2018; Johnson et al., 2020).**

For a better understanding of this triple relation a new "diet-microbe-disease" and "diet-metabolite-disease" interactions concept has appeared, these interactions are more complicated than previously recognized relationships between important nutrients and illness, which focused on single-nutrient connections. The synthesis of diet-derived metabolites such short chain fatty acids (SCFAs) or the creation of secondary metabolites produced by bacteria prior to entering host circulation are likely to have a role in microbe-disease interactions **(Fig. 45) (Johnson et al., 2020).**

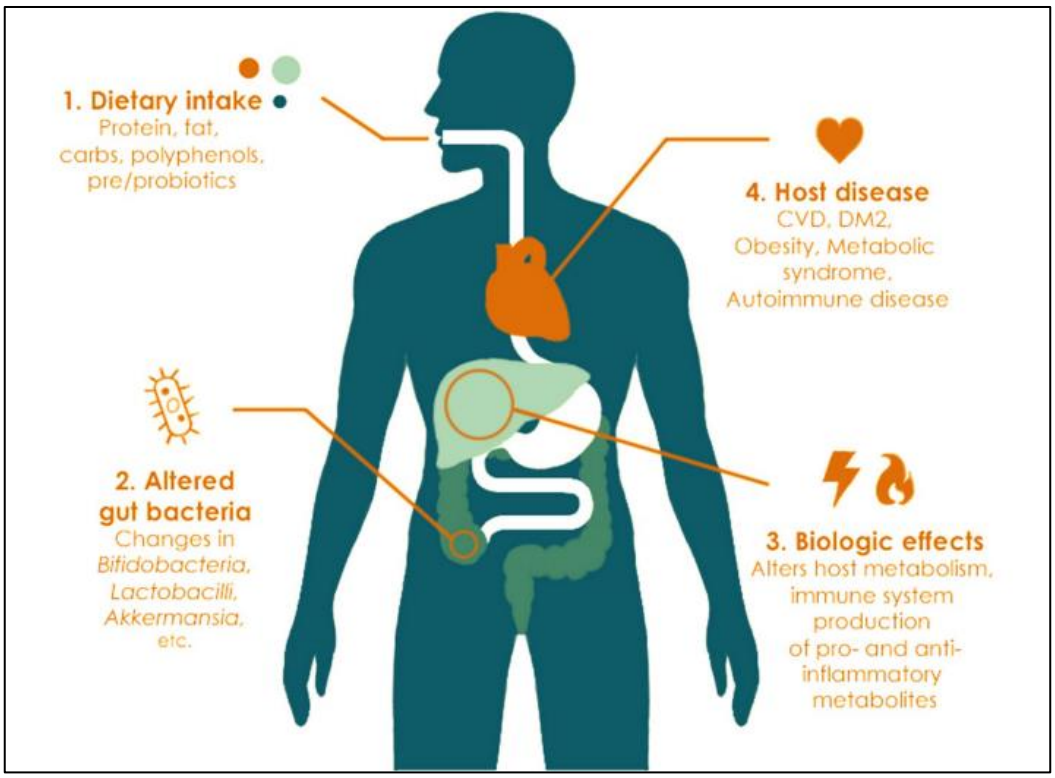


Fig. 45 Dietary factors influence the gut microbiota and human health (Singh et al., 2017).

The nature of the relationship between human health and the gut microbiota is one of the most pressing issues in medicine today **(Hills et al., 2019).** According to Recent research indicates that the gut microbiome is essential in regulating the risk of various chronic illnesses, as well as in medication metabolism (5). Given this association, dietary manipulation of microbial composition may have significant therapeutic potential **(Singh et al., 2017)**.

Moving forward, the challenge will be to show evidence for dietary changes on the gut microbiota that have significant impact on human physiology **(Albenberg et al., 2014).**The effects of various common food components on the gut microbiota are illustrated in **(Table 5)** which shows that consuming certain types of food causes predictable changes in existing host bacterial species and that altering them may influence disease activity, with significant consequences for human health **(Singh et al., 2017).**

Table 5. Complexity of diet–microbiome–health crosstalk (Zmora et al., 2019).

Dietary component	Bacteria	Metabolites or mediators	Disease risk
Red meat (l-carnitine)	Prevotella[a]	↑ TMAO	↑ CVD
Red meat (l-carnitine)	Bacteroides[b]	↓ TMAO	↓ CVD
Emulsifiers (lecithin	?	↑ TMAO	↑ CVD
Emulsifiers (P80 and CMC)	↑ Proteobacteria[a]	↑ LPS and flagellin	↑ Colitis and metabolic syndrome
Emulsifiers (P80 and CMC)	↑ Akkermansia[a]	↑ LPS and flagellin	↑ Colitis and metabolic syndrome
Red meat (heterocyclic amines)	Bacteroides[a]	↑ 7-OHIQ	↑ Carcinogenesis
Red meat (heterocyclic amines)	Clostridium[a]	↑ 7-OHIQ	↑ Carcinogenesis
Red meat (heterocyclic amines)	Eubacterium[a]	↑ 7-OHIQ	↑ Carcinogenesis
Red meat (heterocyclic amines)	Lactobacillus[b]	↑ IQ and PhIP	↓ Carcinogenesis
Red meat (haem)	↑ Bacteroides[a]	↑ LPS?	↑ Colon cancer

Red meat (haem)	↑ Sulfate-reducing bacteria[a]	↑ Hydrogen sulfide	↑ Colon cancer
Red meat (haem)	↑ Prevotella[a]	↑ LPS?	↑ Colon cancer
Red meat (haem)	↑ Akkermansiaa	↓ Mucus	↑ Colon cancer and IBD
Polyphenols (caffeic acid)	↑ Akkermansia[b]	?	↓ IBD
Polyphenols (resveratrol)	↓ Prevotella[a]	↓ TMAO	↓ CVD
Polyphenols (grape and/or cranberry extract)	↑ Akkermansia[b]	?	↓ Metabolic syndrome
NAS (saccharin)	↑ Bacteroides[a]	↑ Acetate, propionate and LPS[a]	↑ Metabolic syndrome
NAS (saccharin)	↓ Akkermansia[b]	↑ Acetate and propionate[a]	↑ Metabolic syndrome
NAS (saccharin)	↑ Turicibacter[a]	↑ LPS?	↑ Metabolic syndrome
NAS (aspartame)	↑ Clostridium leptum[a]	↑ Acetate, propionate and butyrate[a]	↑ Metabolic syndrome
NAS (acesulfame-potassium)	↑ Bacteroides[a]	↑ LPS, pyruvate and cholate	↑ Metabolic syndrome
High- fat and high- sugar diet	↑ Firmicutes, Mollicutes and Eubacterium[a]	↑ Lactate, acetate and butyrate[a]	↑ Metabolic syndrome
High- fat and high- sugar diet	↓ Bacteroidetes[b]	?	↑ Metabolic syndrome
Saturated fat	↑ Bacteroides and Turicibacter[a]	↑ LPS	↑ Metabolic syndrome
Saturated fat	Supplemented Bacteroides uniformis[b]	?	↓ Metabolic syndrome

Saturated fat	↑ Bilophila[a]	↑ LPS	↑ IBD
Saturated fat	↓ S24-7 (Bacteroidetes) and Lachnospiraceae[b]	↓ Butyrate and retinoic acid[b]	↑ IBD
Saturated fat	↑ Bacteroides, Mollicutes and Lactobacillus[a]	↓ Flavonoids and UCP1	↑ Metabolic syndrome
Saturated fat (palmitate)	↓ S24-7 (Bacteroidetes) and Prevotellaceae[b]	↓ Propionate?[b]	↑ Multiple sclerosis
Unsaturated fat	↑ Akkermansia, Mollicutes and Lactobacillus[b]	↓ LPS?	↓ Metabolic syndrome
High- fat (saturated and unsaturated)	↓ Prevotella, Bacteroides and Turicibacter[a]	↓ Pro- IL-1β	↓ Osteomyelitis
Fibre	Clostridiales[a]	↑ Butyrate[a]	↑ Colon cancer
Fibre	?	↑ Butyrate, IL-10 and IL-18[b]	↓ Colon cancer
Fibre	↑ Actinobacteria and Bacteroidetes[b]	↑ Propionate, butyrate and IGN[b]	↓ Metabolic syndrome
Fibre	Prevotella[b]	↑ Glycogen storage	↓ Metabolic syndrome
Fermentable fibre (inulin)	↑ Bifidobacterium and Akkermansia[b]	↑ IL-22	↓ Metabolic syndrome
Fermentable fibre (inulin)	Bifidobacterium[b]	↑ Mucus growth	↓ IBD
Fermentable fibre (inulin)	?	↑ Acetate[b] ↓ Appetite	↓ Metabolic syndrome

High- fat	?	↑ Acetate[a], GSIS and hyperphagia	↑ Metabolic syndrome
Low- fibre diet	↑ Akkermansia and Bacteroides caccae[a]	↓ Mucus	↑ Citrobacter susceptibility

CMC, carboxymethyl cellulose; CVD, cardiovascular disease; GSIS, glucose- stimulated insulin secretion; IGN, intestinal gluconeogenesis; LPS, lipopolysaccharide; NAS, non-caloric artificial sweetener; P80, polysorbate-80; IQ and 7-OHIQ, 2-amino-3- methyl-3H- imidazo[4,5-f] quinoline and its 7-keto derivative, respectively ; PhIP, 2-amino-1-methyl-6 phenylimidazo(4,5-b)pyridine; TMAO, trimethylamine *N*- oxide; UCP1, mitochondrial brown fat uncoupling protein 1. [a]Associations detrimental to host health.[b]Associations beneficial to host health.

As an easily changeable environmental component, dietary treatments with significant impacts on human health, such as the personalized nutritional regulation of the gut microbiota, may eventually provide effective approaches to disease prevention and therapy **(Leeming et al., 2021; Albenberg et al., 2014).**

Unfortunately, specific understanding on how to use diet as an actionable tool is still limited. Due to the field's relative newness, techniques have yet to be standardized, resulting in highly diverse study findings. This might be due to variables associated with the challenges of accurately representing both food and gut flora **(Leeming et al., 2021).**

The complexity of each individual's gastrointestinal tract's shifting environment has also proven challenging to examine. With each person's microbiome functioning as an ecosystem, the majority of mechanisms describing how food affects the microbiome and how the microbiome affects dietary inputs to effect health remain unclear and the studies along this remain continue **(Singh et al., 2017; Johnson et al., 2020).**

Conclusion and Perspectives

Conclusion and Perspectives

"All disease begins in the gut" That's what Hippocrates said over 2,000 years ago. Decades after, Studies became steps closer to proving this hypothesis.

The gastrointestinal tract is no longer thought of simply as a "tube" through which nutrients are digested and absorbed; instead, substances passing through it have the potential to interact with our microbiota, causing changes in its stability and dynamic, and thus affecting human health in both positive and negative ways.

Understanding the relationship between food and the gut microbiota, their interactions, and how each modulates the other is critical for successful promotion of human health. Data collected over the past decade emphasize the important effect of dietary factors, like fibers and fermented food, as modulators of microbiota composition. Changes in the diet pattern even for a short duration of time induce drastic effects on the gut microbiota, which may further affect human physiology and disease processes.

These findings open the door to developing dietary strategies aimed at modulating the microbiota in order to improve human health; nevertheless, further researches are needed to confirm the mechanism by which bacterial diversity alternation interact with diseases and metabolic disturbances, as well as its relationship with food intake.

It could be interesting, for example, to study the effects of a higher intake of local fermented food, such as traditional cheese, to better comprehend its beneficial role in the modification of the composition of the human gut microbiota and eventual prophylactic and therapeutic role, therefore designing a dietary pattern based on the result of this study, the thing that we aim to do if we had the chance to.

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Net 03: https://biospecnutritionals.com/health-topics/gut-health-and-gastrointestinal-gi-imbalances/

Net 04 : https://psychscenehub.com/psychinsights/gut-microbiome-and-depression-pathophysiology-role-of-pre-and-probiotics-2/

Abstract

The digestive system of the human is inhabited by trillion of diverse groups of microorganisms including symbiotic, opportunistic pathogens and commensal organisms. All these microbes are collectively named gut microbiome (GM). This microbiota is a changing ecosystem continuously shaped by many factors, such as mode of infant delivery and feeding methods, age, geography, stress, and antibiotics use in addition to dietary habits, being one of the major influences.

The GM plays a major role in digesting food to produce an extensive range of microbial metabolites that may have an important impact on human physiology. Reciprocally, dietary components including macronutrients, micronutrients and food additives, modulate the composition and functional capacity of the gut microbiota, causing either positive or negative effects on human health. However, nutrients are rarely consumed independently and research on diet-microbiota relationship has progressively moved from the study of individual dietary components towards overall dietary patterns (i.e., Western-type, vegan and vegetarian, and Mediterranean diets).

The balance between the gut microbial species is depending on the human daily diet. Therefore, the unbalanced diet may lead to the progress and development of human diseases. These include metabolic and inflammatory disorders, cancer, as well as diabetes. The present review aimed to focus on how interactions between food components and gut microbiota may influence or even determine human health and disease.

Keywords: Gut microbiome, diet, human health, disease.

Résumé

Le système digestif de l'homme est habité par des milliards de groupes divers de micro-organismes, y compris des agents pathogènes symbiotiques, opportunistes et des organismes commensaux. Tous ces microbes sont collectivement appelés microbiome intestinal. Ce microbiote est un écosystème en constante évolution façonné par de nombreux facteurs, tels que le mode d'accouchement et les méthodes d'alimentation du nourrisson, l'âge, la géographie, le stress et l'utilisation d'antibiotiques en plus des habitudes alimentaires, étant l'une des influences majeures.

Le microbiote intestinal joue un rôle majeur dans la digestion des aliments pour produire une vaste gamme de métabolites microbiens qui peuvent avoir un impact important sur la physiologie humaine. Réciproquement, les composants alimentaires, notamment les macronutriments, les micronutriments et les additifs alimentaires, modulent la composition et la capacité fonctionnelle de ce microbiote, provoquant des effets positifs ou négatifs sur la santé humaine. Cependant, les nutriments sont rarement consommés indépendamment et la recherche sur la relation alimentation-microbiote s'est progressivement déplacée de l'étude des composants alimentaires individuels vers les schémas alimentaires globaux (c'est-à-dire les régimes végétaliens et végétariens, les régimes de type occidental, et les régimes méditerranéens).

L'équilibre entre les espèces microbiennes intestinales dépend de l'alimentation quotidienne de l'homme. Par conséquent, une alimentation déséquilibrée peut entraîner la progression et le développement de maladies humaines. Ceux-ci comprennent les troubles métaboliques et inflammatoires, le cancer, ainsi que le diabète. La présente revue visait à se concentrer sur la façon dont les interactions entre les composants alimentaires et le microbiote intestinal peuvent influencer ou même déterminer la santé et les maladies humaines.

Mots-clés : Microbiome intestinal, alimentation, santé humaine, maladie.

ملخص

يسكن الجهاز الهضمي للإنسان تريليونات من مجموعات متنوعة من الكائنات الحية الدقيقة بما في ذلك مسببات الأمراض والكائنات الحية المتعايشة. كل هذه الميكروبات تسمى ميكروبيوم الأمعاء. تعد هذه الكائنات الحية الدقيقة نظامًا بيئيًا مستمر التغير من خلال العديد من العوامل، مثل طريقة الولادة وطرق تغذية الرضيع، العمر، الجغرافيا، التوتر واستخدام المضادات الحيوية بالإضافة إلى العادات الغذائية، كونها أحد العوامل الرئيسية المؤثرة.

تلعب بكتيريا الأمعاء دورًا رئيسيًا في هضم المواد الغذائية لإنتاج مجموعة واسعة من المستقلبات الميكروبية التي قد يكون لها تأثير مهم على فسيولوجيا الإنسان. بالمقابل، فإن المكونات الغذائية بما في ذلك المغذيات الكبيرة، المغذيات الدقيقة والمضافات الغذائية، تعدل التركيب والقدرة الوظيفية لميكروبات الأمعاء، مما يتسبب في تأثيرات إيجابية أو سلبية على صحة الإنسان. ومع ذلك، نادرًا ما يتم استهلاك العناصر الغذائية بشكل مستقل، لذا انتقلت الأبحاث حول العلاقة بين النظام الغذائي والبكتيريا تدريجياً من دراسة المكونات الغذائية الفردية إلى الأنماط الغذائية الشاملة (أي الأنظمة الغذائية الغربية، والنباتية، والمتوسطية).

يعتمد التوازن بين الأنواع الميكروبية في الأمعاء على النظام الغذائي اليومي للإنسان. لذلك فإن النظام الغذائي غير المتوازن قد يؤدي إلى تطور الأمراض. وهذا يشمل الاضطرابات الأيضية والالتهابية والسرطان وكذلك مرض السكري. هدفت المراجعة الحالية إلى التركيز على كيفية تأثير التفاعلات بين مكونات الغذاء وميكروبات الأمعاء وانعكاسها على صحة الإنسان.

الكلمات المفتاحية: ميكروبيوم الأمعاء، النظام الغذائي، صحة الإنسان، المرض.

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The Effect of Diet on Gut Microbiota

Abstract

The digestive system of the human is inhabited by trillion of diverse groups of microorganisms including symbiotic, opportunistic pathogens and commensal organisms. All these microbes are collectively named gut microbiome (GM). This microbiota is a changing ecosystem continuously shaped by many factors, such as mode of infant delivery and feeding methods, age, geography, stress, and antibiotics use in addition to dietary habits, being one of the major influences.

The GM plays a major role in digesting food to produce an extensive range of microbial metabolites that may have an important impact on human physiology. Reciprocally, dietary components including macronutrients, micronutrients and food additives, modulate the composition and functional capacity of the gut microbiota, causing either positive or negative effects on human health. However, nutrients are rarely consumed independently and research on diet-microbiota relationship has progressively moved from the study of individual dietary components towards overall dietary patterns (i.e., Western-type, vegan and vegetarian, and Mediterranean diets).

The balance between the gut microbial species is depending on the human daily diet. Therefore, the unbalanced diet may lead to the progress and development of human diseases. These include metabolic and inflammatory disorders, cancer, as well as diabetes. The present review aimed to focus on how interactions between food components and gut microbiota may influence or even determine human health and disease.

Keywords: Gut microbiome, diet, human health, disease.

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