Izbor i upotreba probiotika

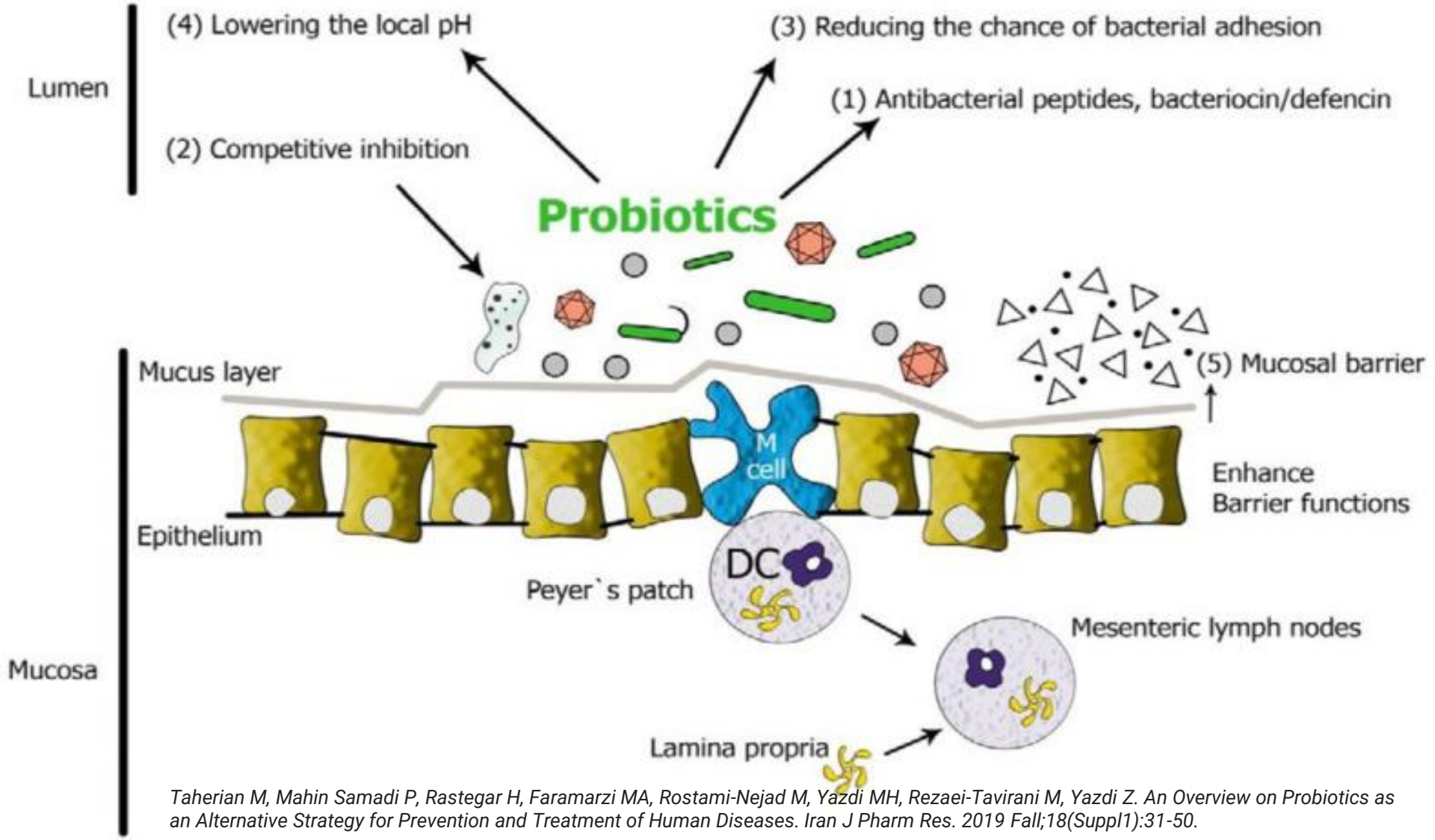
Prim dr Vesna Đurić

Prof dr Dušan Djurić

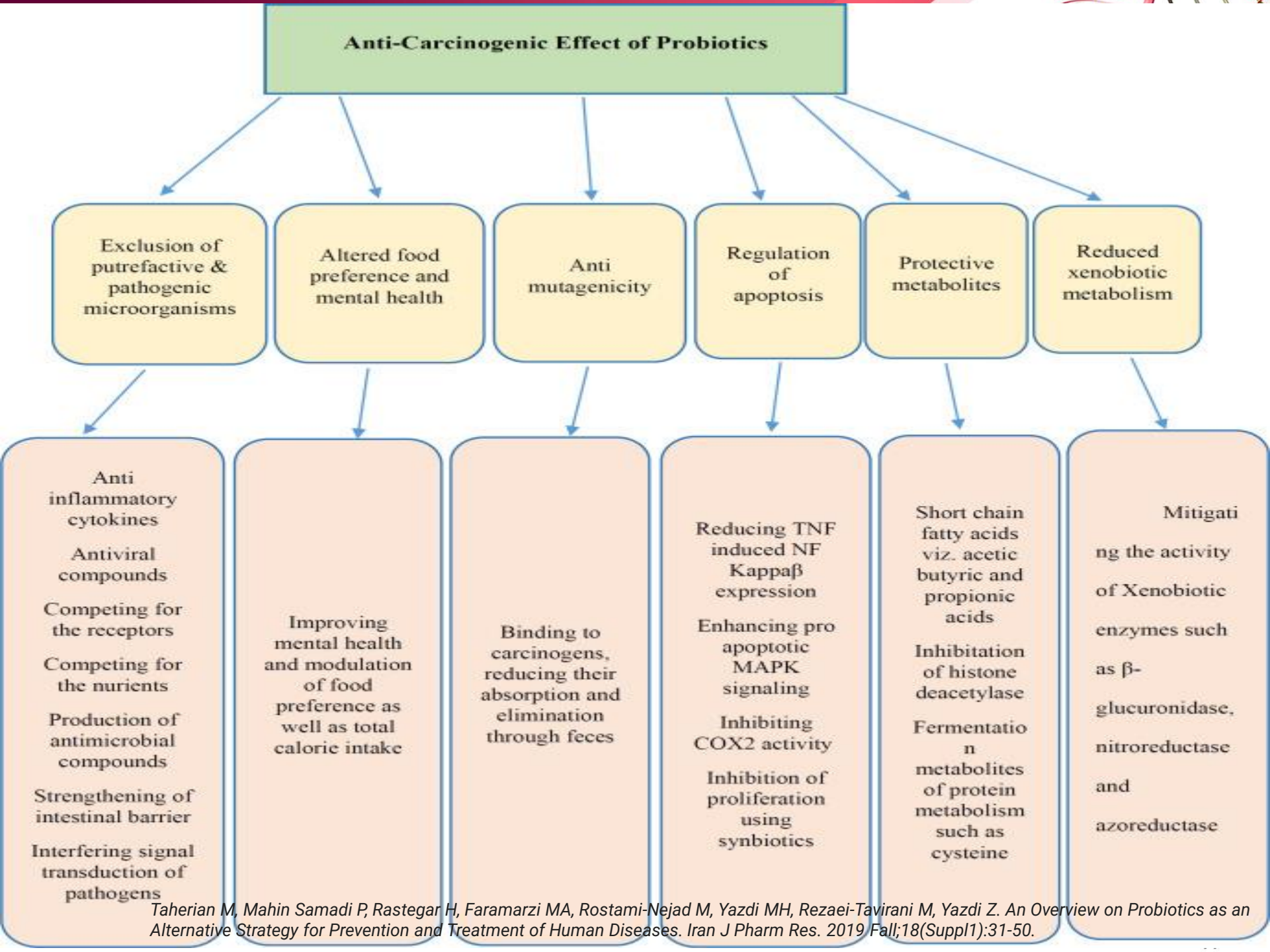
Definicija

- *The International Scientific Association for Probiotics and Prebiotics*definiše probiotike kao **„žive mikroorganizme koji, kada se daju u adekvatnim količinama, daju zdravstvenu korist domaćinu“**.
  - Ovi mikroorganizmi, koji se sastoje uglavnom od bakterija, ali, takođe, uključuju kvasce, prirodno su prisutni u fermentisanoj hrani, mogu se dodati drugim prehrambenim proizvodima i dostupni su kao dijetetski suplementi.
  - Međutim, nemaju sve namirnice i dijetetski suplementi označeni kao probiotici na tržištu dokazane zdravstvene prednosti.

Inhibicija patogenih bakterija i povećana zaštita creva probioticima; Opšti obrazac interferencije između probiotika i crevne sluzokože

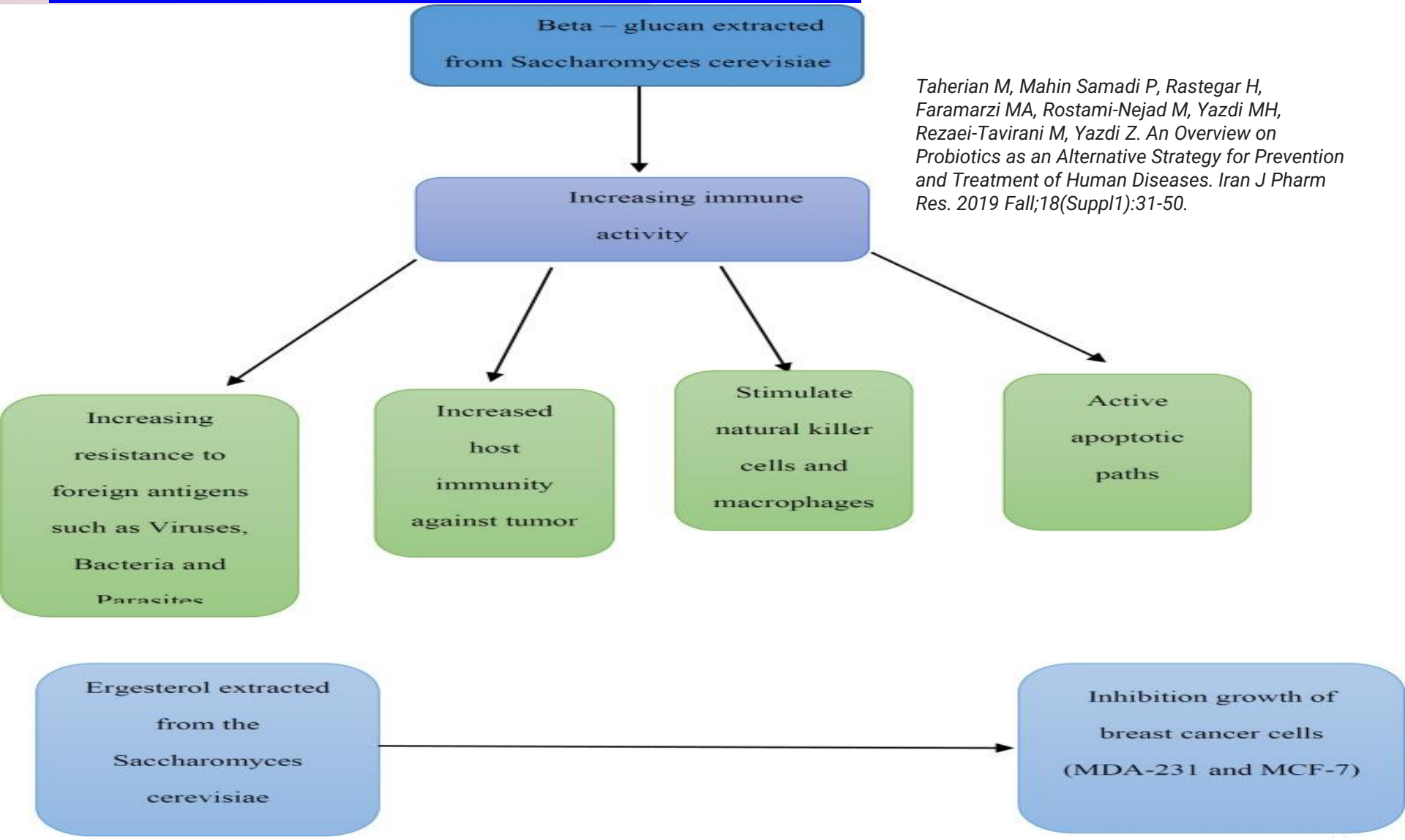


Taherian M, Mahin Samadi P, Rastegar H, Faramarzi MA, Rostami-Nejad M, Yazdi MH, Rezaei-Tavirani M, Yazdi Z. An Overview on Probiotics as an Alternative Strategy for Prevention and Treatment of Human Diseases. Iran J Pharm Res. 2019 Fall;18(Suppl1):31-50.



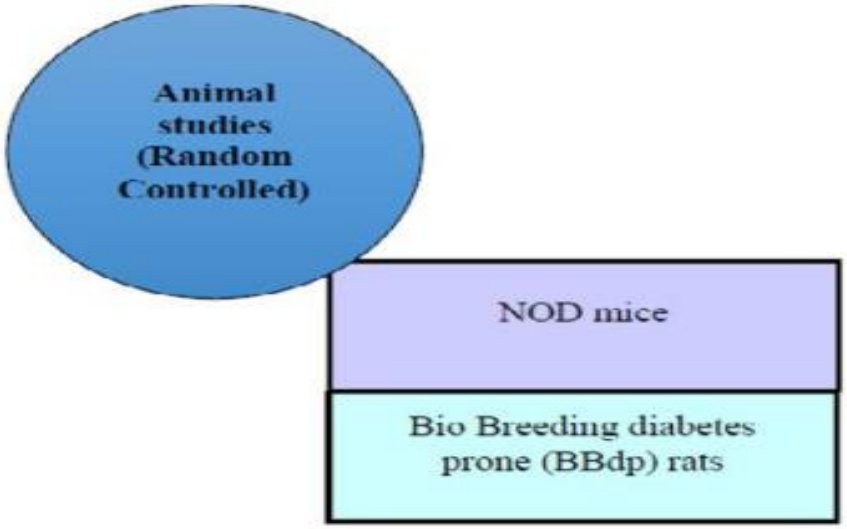
Taherian M, Mahin Samadi P, Rastegar H, Faramarzi MA, Rostami-Nejad M, Yazdi MH, Rezaei-Tavirani M, Yazdi Z. An Overview on Probiotics as an Alternative Strategy for Prevention and Treatment of Human Diseases. Iran J Pharm Res. 2019 Fall;18(Suppl1):31-50.

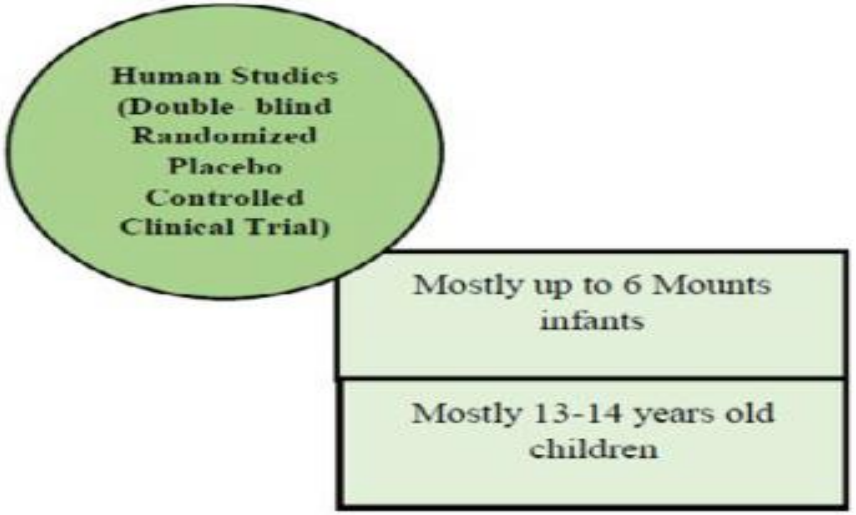
Jedinjenja iz kvasca i njihovo dejstvo na kancer

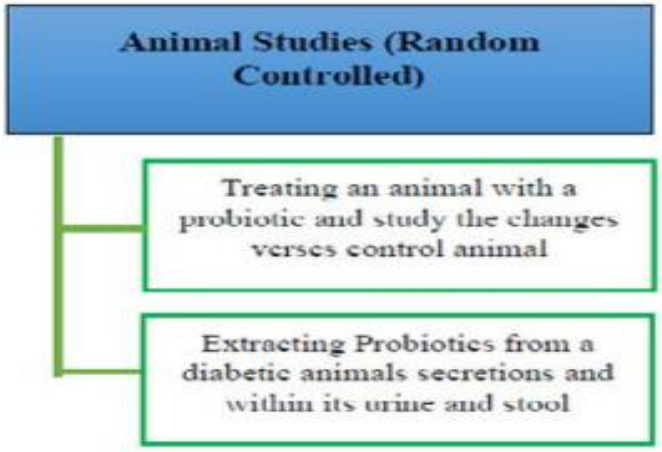


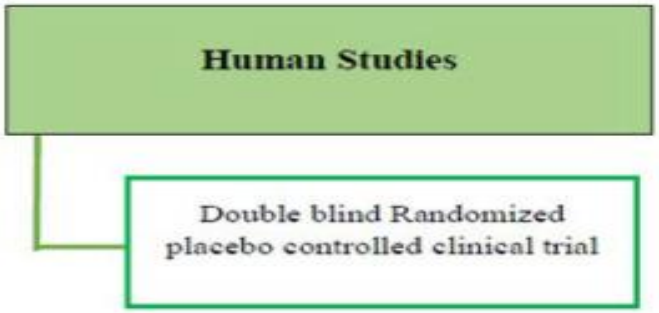
Taherian M, Mahin Samadi P, Rastegar H, Faramarzi MA, Rostami-Nejad M, Yazdi MH, Rezaei-Tavirani M, Yazdi Z. An Overview on Probiotics as an Alternative Strategy for Prevention and Treatment of Human Diseases. Iran J Pharm Res. 2019 Fall;18(Suppl1):31-50.

Studije na ljudima i životinjama



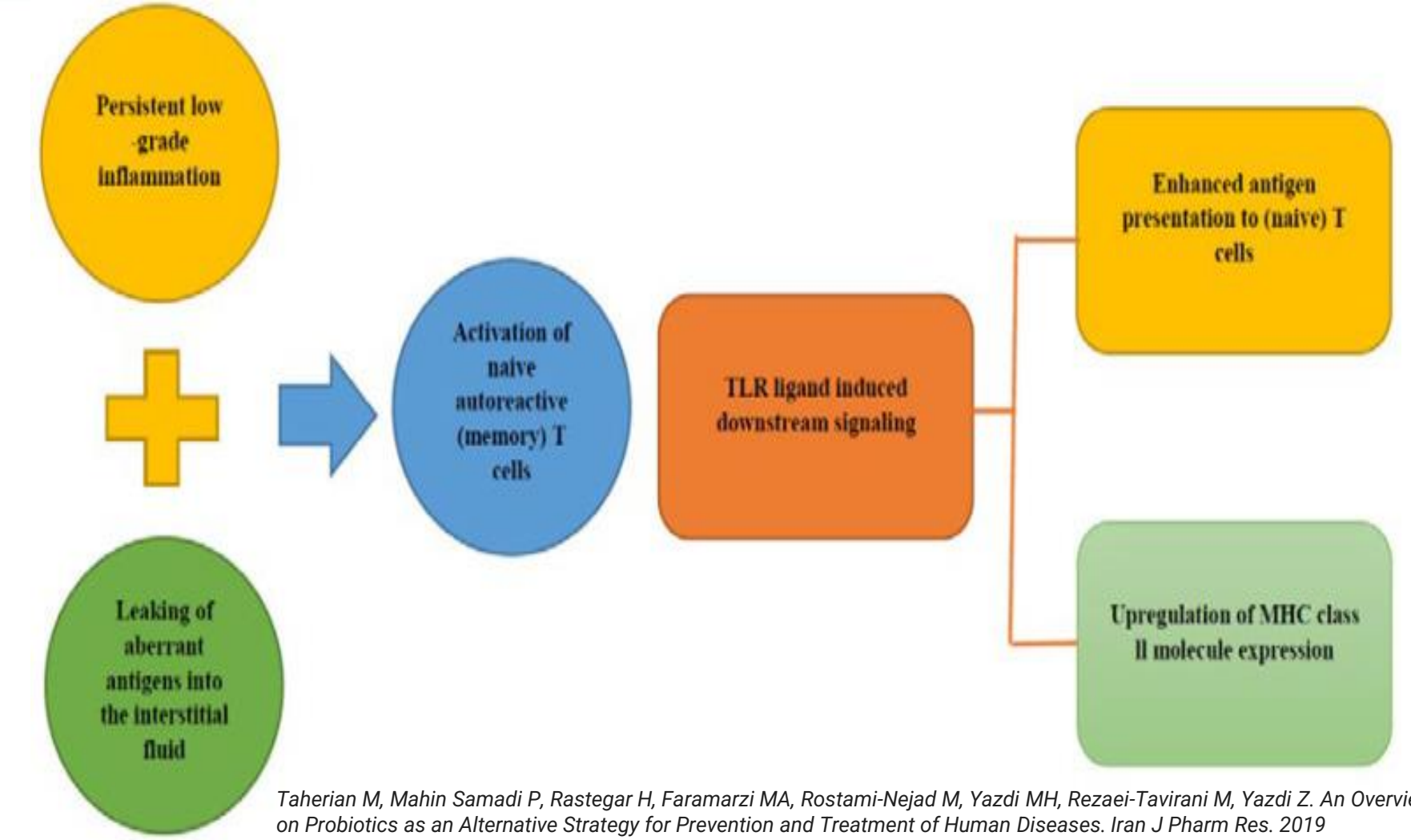






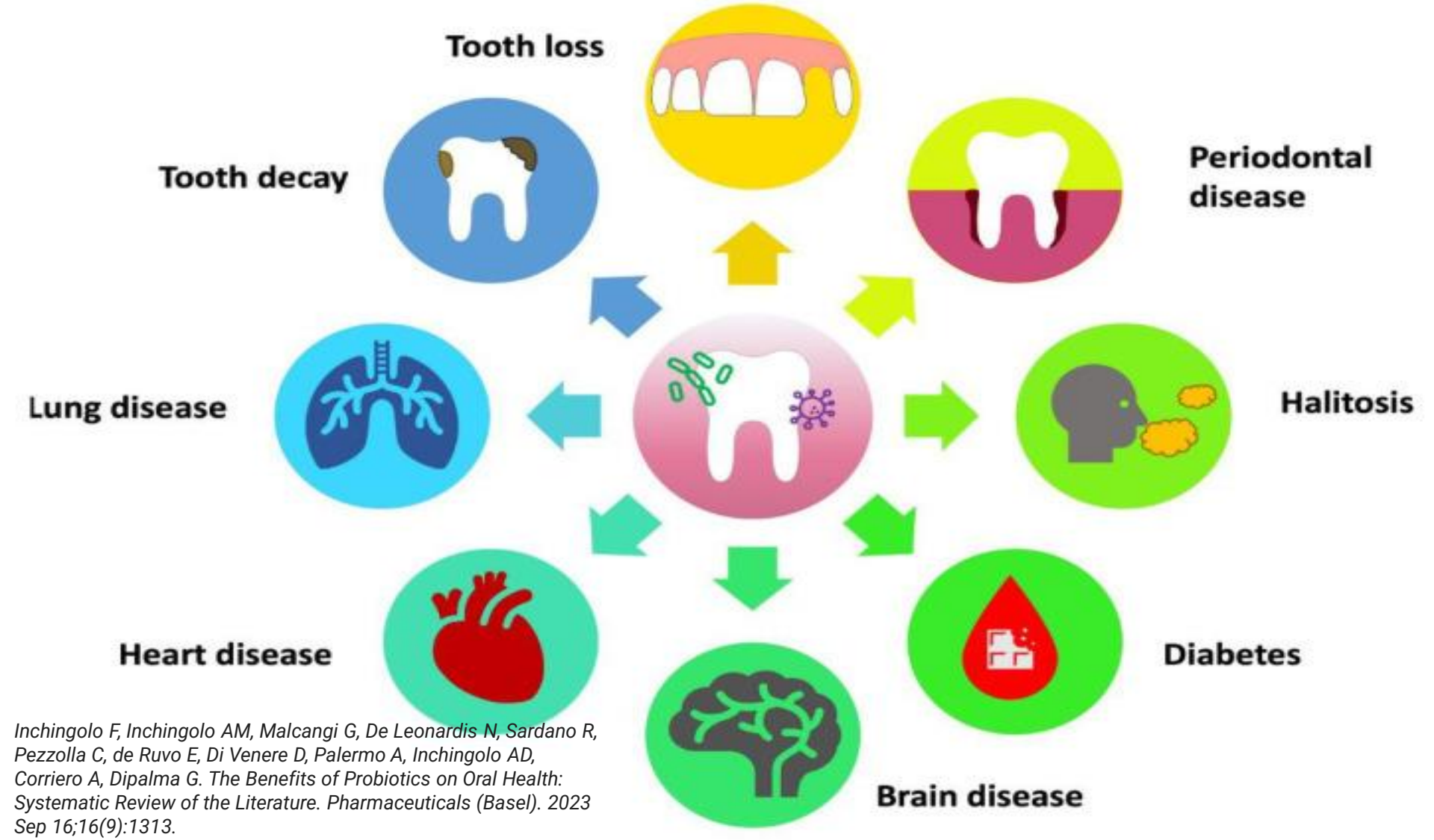
Taherian M, Mahin Samadi P, Rastegar H, Faramarzi MA, Rostami-Nejad M, Yazdi MH, Rezaei-Tavirani M, Yazdi Z. An Overview on Probiotics as an Alternative Strategy for Prevention and Treatment of Human Diseases. Iran J Pharm Res. 2019 Fall;18(Suppl1):31-50.

Nishodni signalizacijski događaji izazvani TLR ligandom uključuju pojačanu regulaciju ekspresije molekula MHC klase II i povećavaju prezentaciju antigena T-ćelija

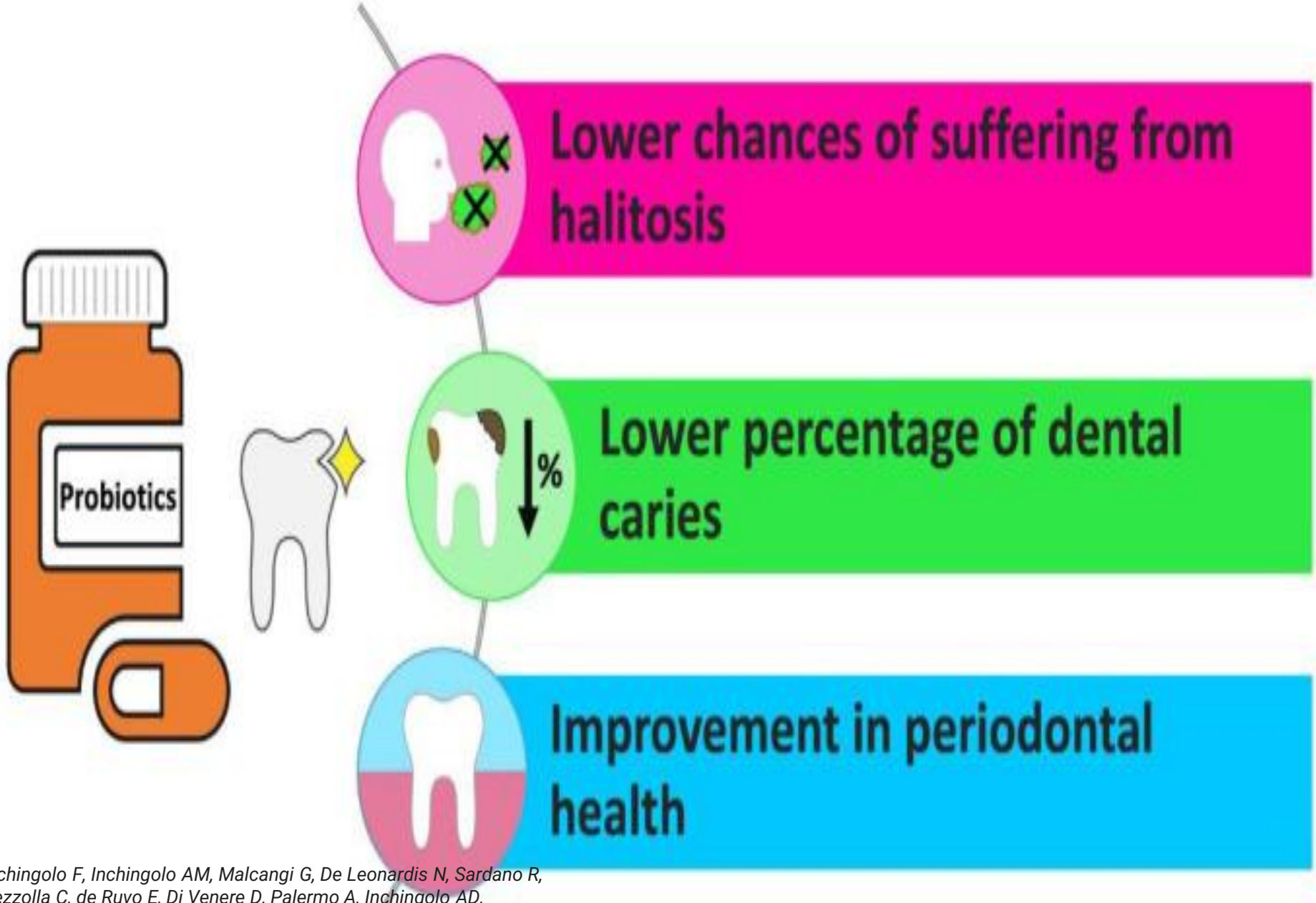


Taherian M, Mahin Samadi P, Rastegar H, Faramarzi MA, Rostami-Nejad M, Yazdi MH, Rezaei-Tavirani M, Yazdi Z. An Overview on Probiotics as an Alternative Strategy for Prevention and Treatment of Human Diseases. Iran J Pharm Res. 2019 Fall;18(Suppl1):31-50.

Efekti neravnoteže oralne mikrobiote na sistemsko zdravlje



Inchingolo F, Inchingolo AM, Malcangi G, De Leonardis N, Sardano R, Pezzolla C, de Ruvo E, Di Venere D, Palermo A, Inchingolo AD, Corriero A, Dipalma G. The Benefits of Probiotics on Oral Health: Systematic Review of the Literature. Pharmaceuticals (Basel). 2023 Sep 16;16(9):1313.

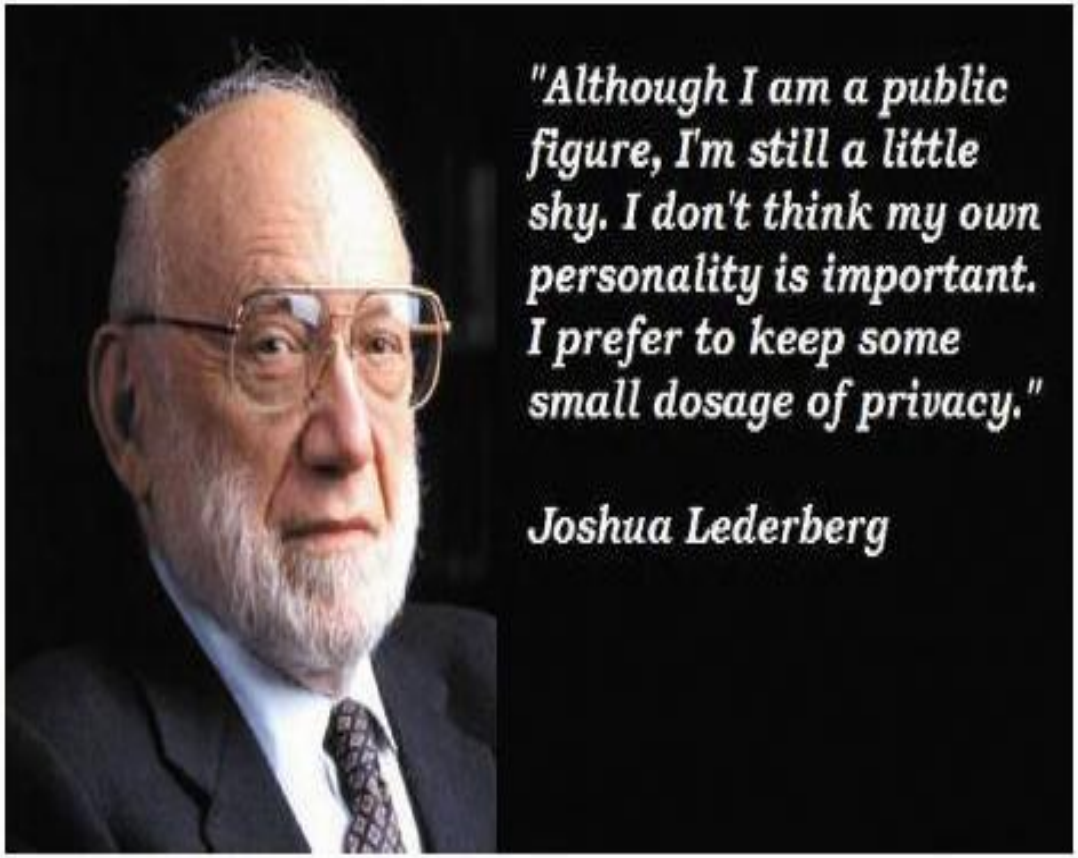


Inchingolo F, Inchingolo AM, Malcangi G, De Leonardis N, Sardano R, Pezzolla C, de Ruvo E, Di Venere D, Palermo A, Inchingolo AD, Corriero A, Dipalma G. The Benefits of Probiotics on Oral Health: Systematic Review of the Literature. Pharmaceuticals (Basel). 2023 Sep 16;16(9):1313.

Nobel Prize 1958

Joshua Lederberg

Medicine/U.S.A.



- ***Biology.*** the totality of microorganisms and their collective genetic material present in or on the human body or in another environment:
  The wide diversity of species that make up the microbiome is hard to fathom.

- coined 2001 by **Joshua Lederberg**,
  American molecular biologist; **micro**(be) + **biome**

A **microbiota** is "the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space"

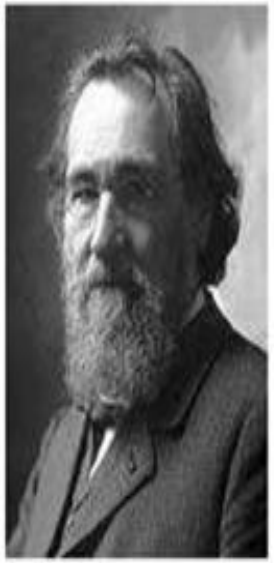
THE NOBEL PRIZE IN CHEMISTRY 1907

Eduard Buchner
Born: 20 May 1860, Died: 13 August 1917
Prize share: 1/1

"for his biochemical researches and his discovery of cell-free fermentation".

Nobel Prize in Physiology or Medicine (1908)

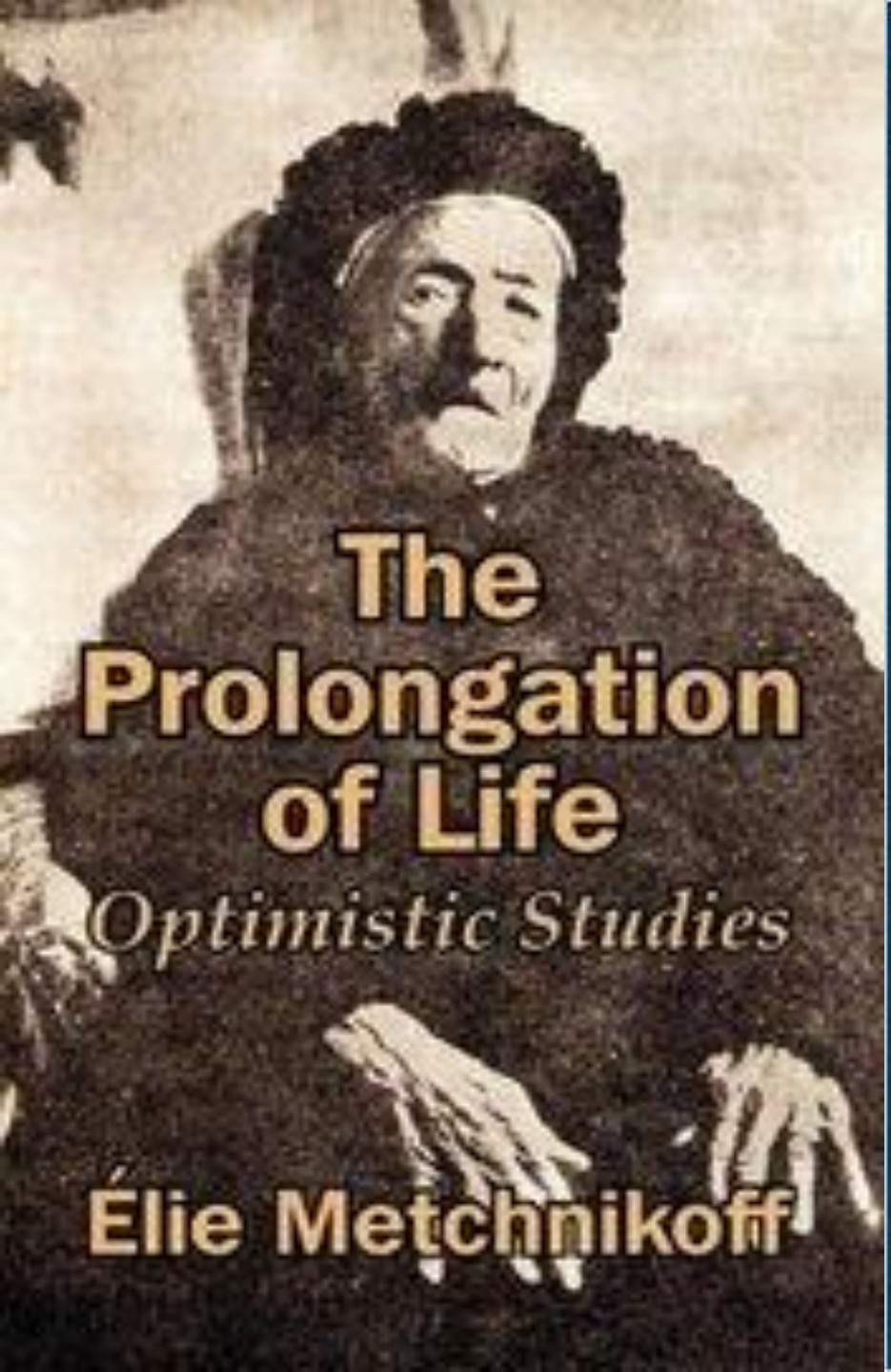
PROBIOTCS



" Russian Nobel prize winner and father of modern immunology, Elie Metchnikoff, a scientist at the Pasteur Institute, was the first to conceptualize Probiotics at the start of the 20th century"

Élie Metchnikoff, 1845-1916 (Russian zoologist)

"in recognition of their work on immunity"

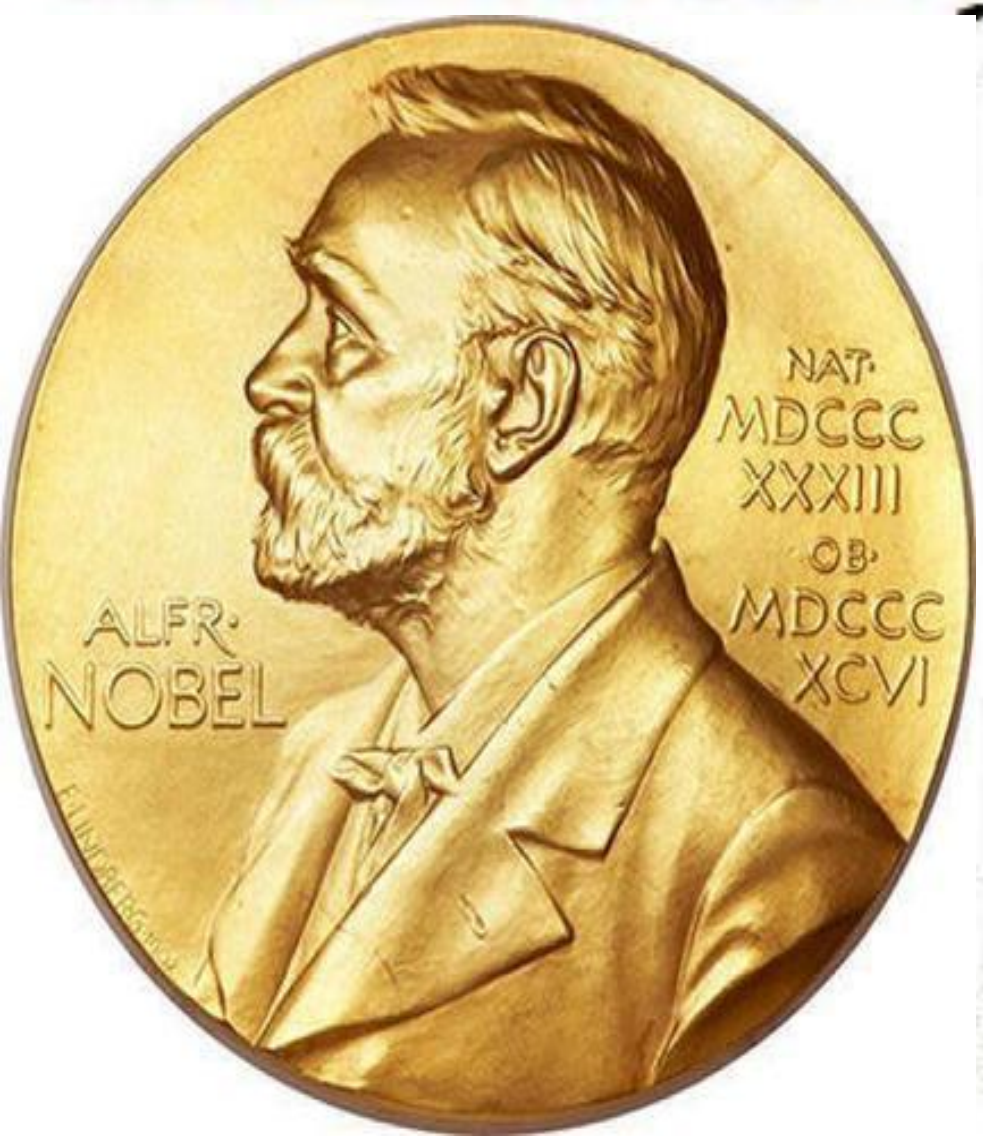


THE
PROLONGATION
OF
LIFE

OPTIMISTIC STUDIES

Élie Metchnikoff

The Nobel Prize in Chemistry 1929



Hans Karl August Simon von Euler-Chelpin

Dr. Minoru Shirota

first launched in Japan in 1935

1

Synthetic digestive fluid test

Original *L. casei* go through synthetic digestive fluid test.

2

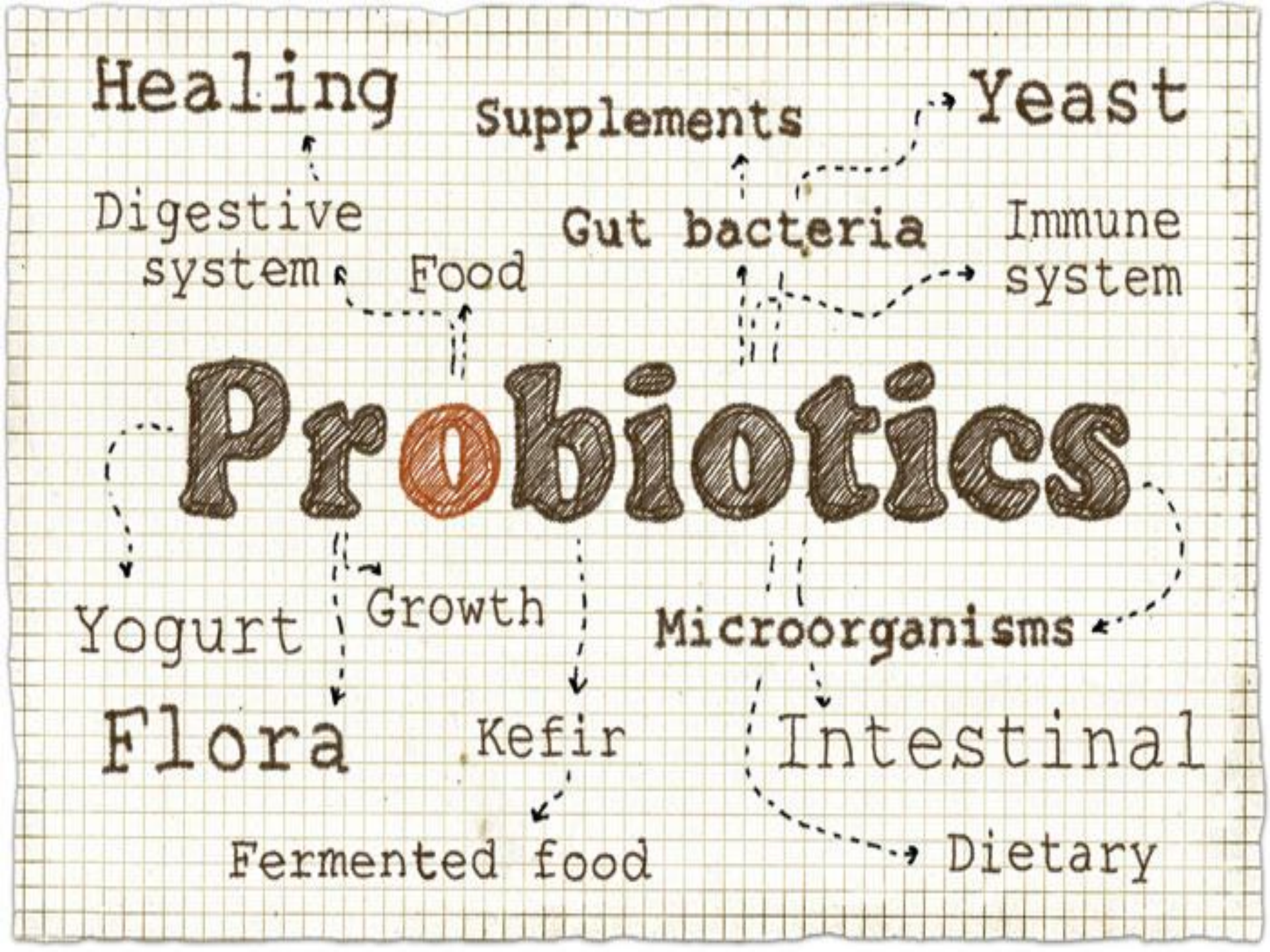
Synthetic digestive fluid is used at increasing concentration

Synthetic digestive fluid(similar to gastric & bile juices) is used at increasing concentration to select stronger *L. casei*.

3

Strongest *L. casei* strain Shirota is selected

Finally the strongest *L. casei* that survives is selected and renamed as **L. casei strain Shirota**.


Healing
Supplements
Yeast
Digestive system
Gut bacteria
Immune system
Food
Probiotics
Yogurt
Growth
Microorganisms
Flora
Kefir
Intestinal
Fermented food
Dietary

Probiotic – History I

- Latin (pro) + Greek (bios) = “**for life”**
- **Kollath** (1953) – “various organic and inorganic supplements that have ability to restore the health of malnourished patients”;
- **Ferdinand Vergin** (1954) – “sctive substances that are essential for a healthy development of life”;
- **Lily** and **Stillwell** (1962) – “the anaerobic bacteria that are able to produce lactic acid and stimulate the growth of other arganisms”;

Probiotic – History II

- **Parker (1974)** – “should include not only microbial organisms but also other supstances that contributed to intestinal microbial balance”;
- **Roy Fuller** (deleted “other substances”) – “live microbial feed supplements which beneficially affects the host animal by improving its intestinal microbial balance”;
- **FAO/WHO (2001)** – “live microorganisms which, when administered in adequate amount, confera health benefit to the host”;

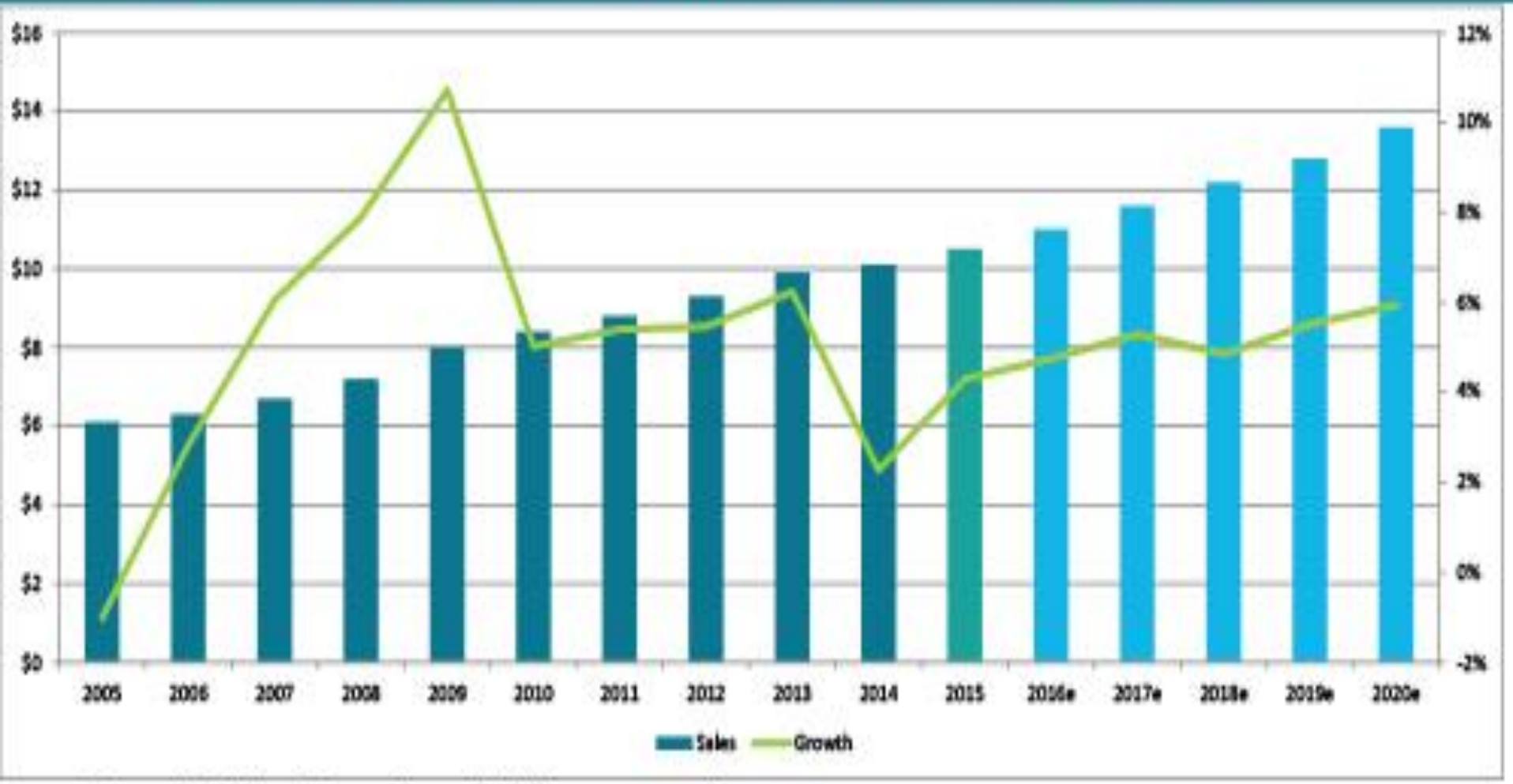
Commercilization of Probiotics

- 1906, “Le Fermente” – **Lactobacilline** (*Streptococcus termophilus + Lactobacillus delbruekii*);
- 1919, Isaac Carasso – commercial production of yogurt in Spain (**Danone**);
- 1935, **Yakult** (*Lactobacillus casei* strain *shirota*)


DANONE
LA FELICIDAD DEL HOGAR..
con DANONE cada dia

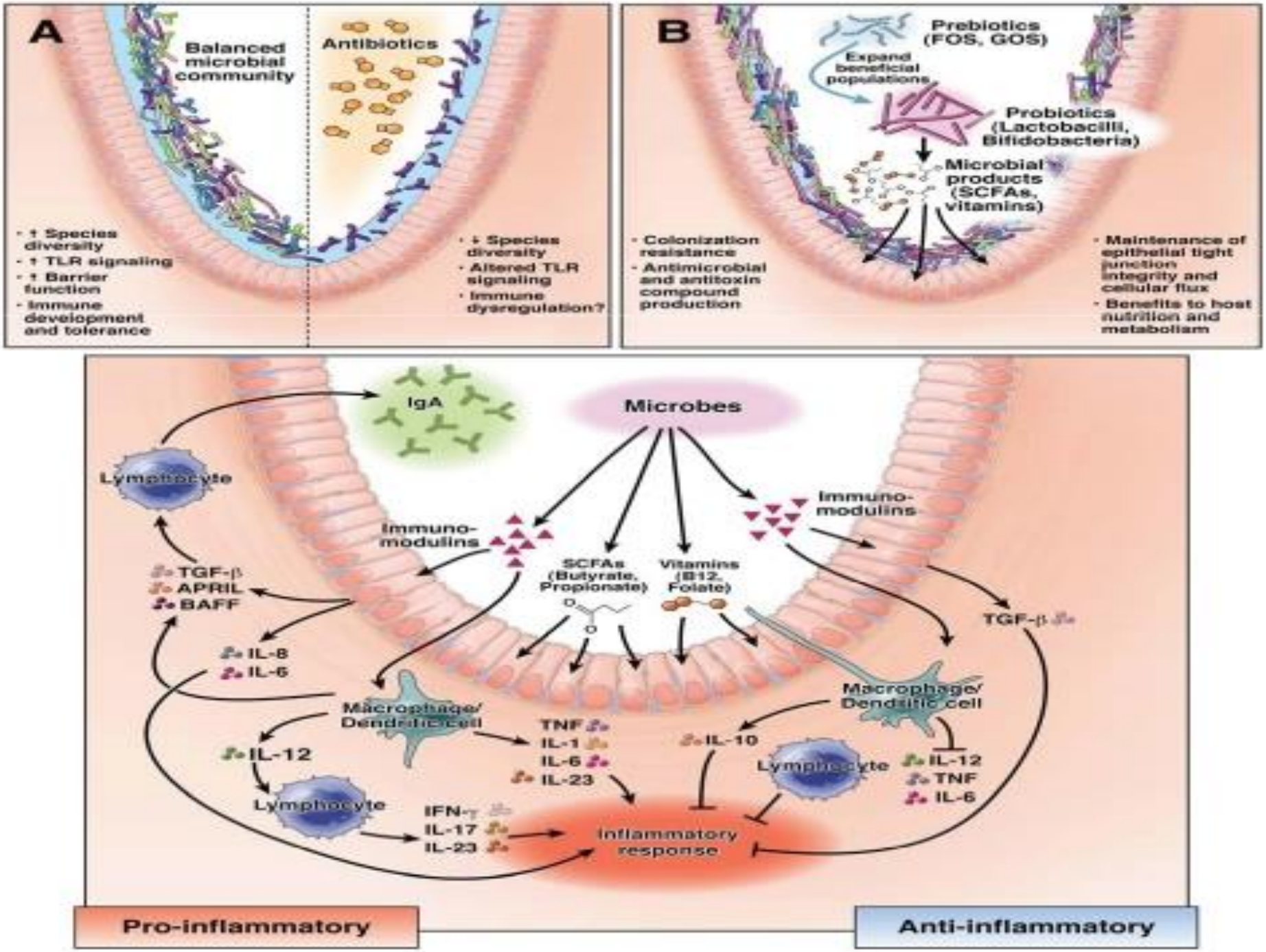

Best if used by:
Nutrition Facts
Nonfat Probiotic Drink
Exclusive Probiotic Strain
Lactobacillus casei
Shirota
Yakult
USA
Keep Refrigerated
5 – 2.7 FL OZ (80 mL) Bottles - 13.5 FL OZ (400 mL)

US Supplement Mass Market Channel Supplement Sales and Growth, 2005-2020e



Source: Nutrition Business Journal ($bil., consumer sales)

The US Supplement Mass Market Channel is expected to grow to $13.6B by 2020 and realize a 5.3% CAGR.


A
Balanced microbial community
Antibiotics
· ↑ Species diversity
· ↑ TLR signaling
· ↑ Barrier function
· Immune development and tolerance
· ↓ Species diversity
· Altered TLR signaling
· Immune dysregulation?
B
Prebiotics (FOS, GOS)
Expand beneficial populations
Probiotics (Lactobacilli, Bifidobacteria)
Microbial products (SCFAs, vitamins)
· Colonization resistance
· Antimicrobial and antitoxin compound production
· Maintenance of epithelial tight junction integrity and cellular flux
· Benefits to host nutrition and metabolism
IgA
Microbes
Lymphocyte
Immuno-modulins
Immuno-modulins
SCFAs (Butyrate, Propionate)
Vitamins (B12, Folate)
TGF-β
APRIL
BAFF
IL-8
IL-6
TGF-β
Macrophage/ Dendritic cell
Macrophage/ Dendritic cell
TNF
IL-1
IL-6
IL-23
IL-12
IL-10
Lymphocyte
Lymphocyte
IL-12
TNF
IL-6
IFN-γ
IL-17
IL-23
Inflammatory response
Pro-inflammatory
Anti-inflammatory

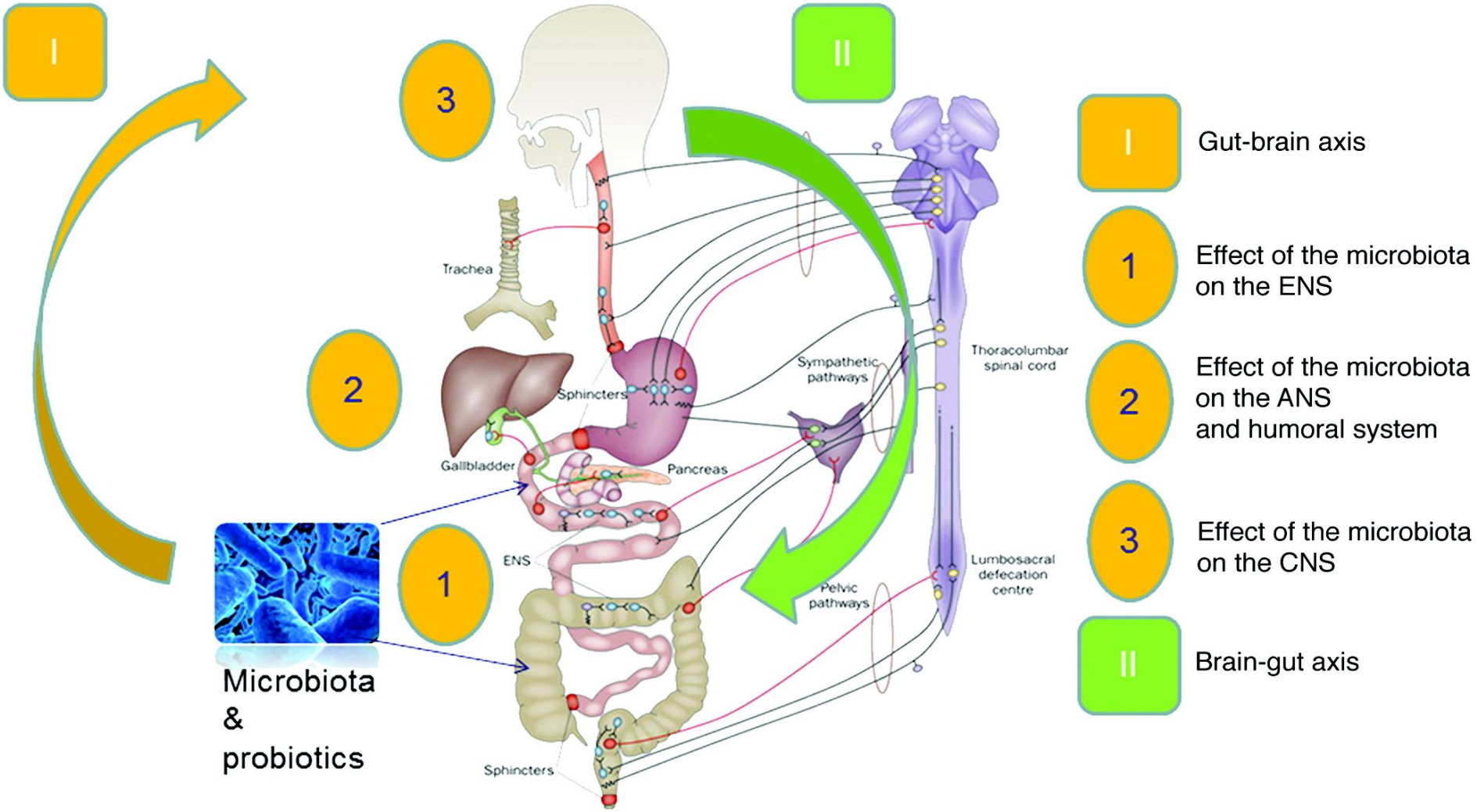


Figure 1. Interaction of the gut microbiome, probiotics and prebiotics on the brain gut axis. Modified from reference 85.

Published in: Delphine M. Saulnier; Yehuda Ringel; Melvin B. Heyman; Jane A. Foster; Premysl Bercik; Robert J. Shulman; James Versalovic; Elena F. Verdu; Ted G. Dinan; Gail Hecht; Francisco Guarner; *Gut Microbes* **2013,** 4, 17-27.
DOI: 10.4161/gmic.22973

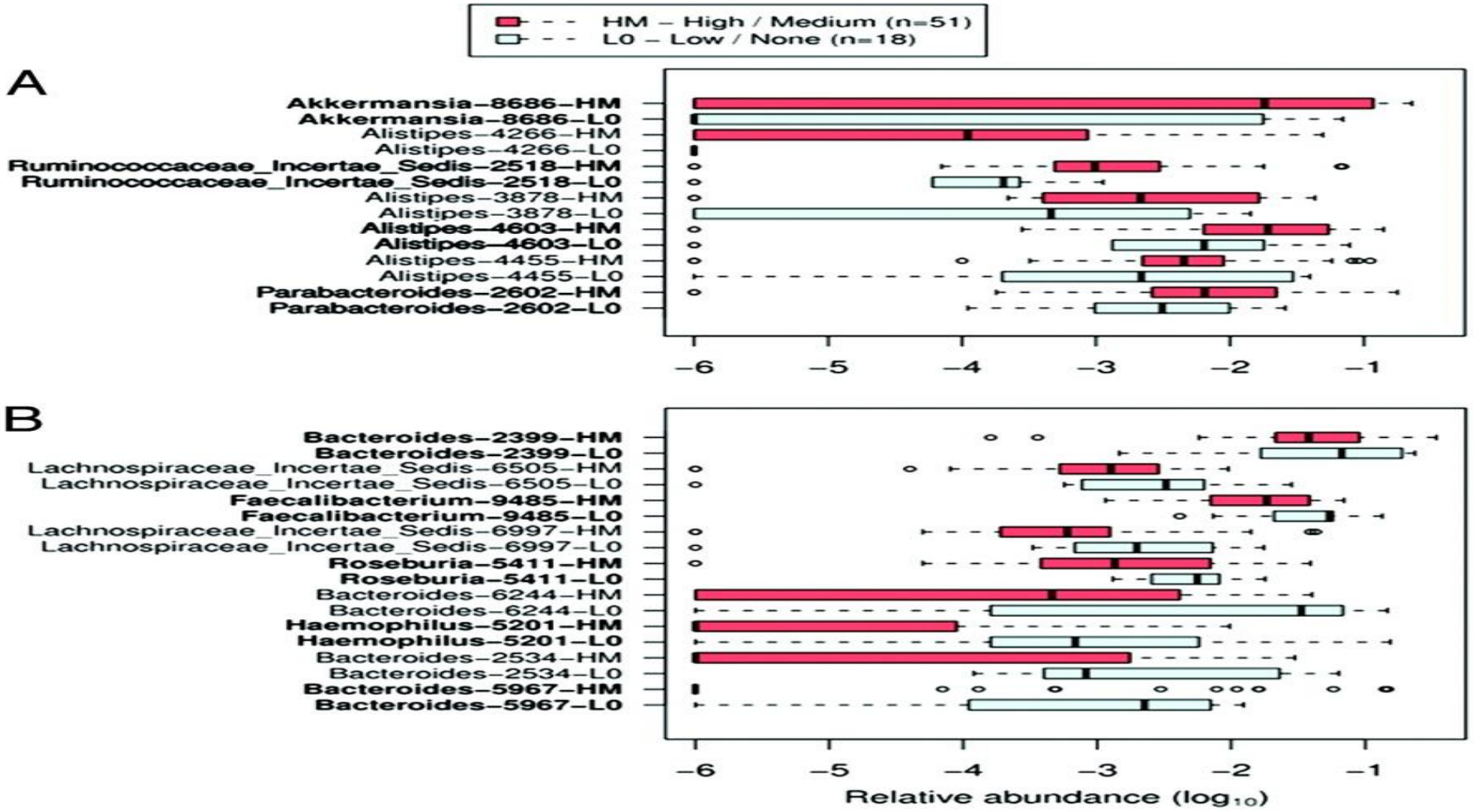
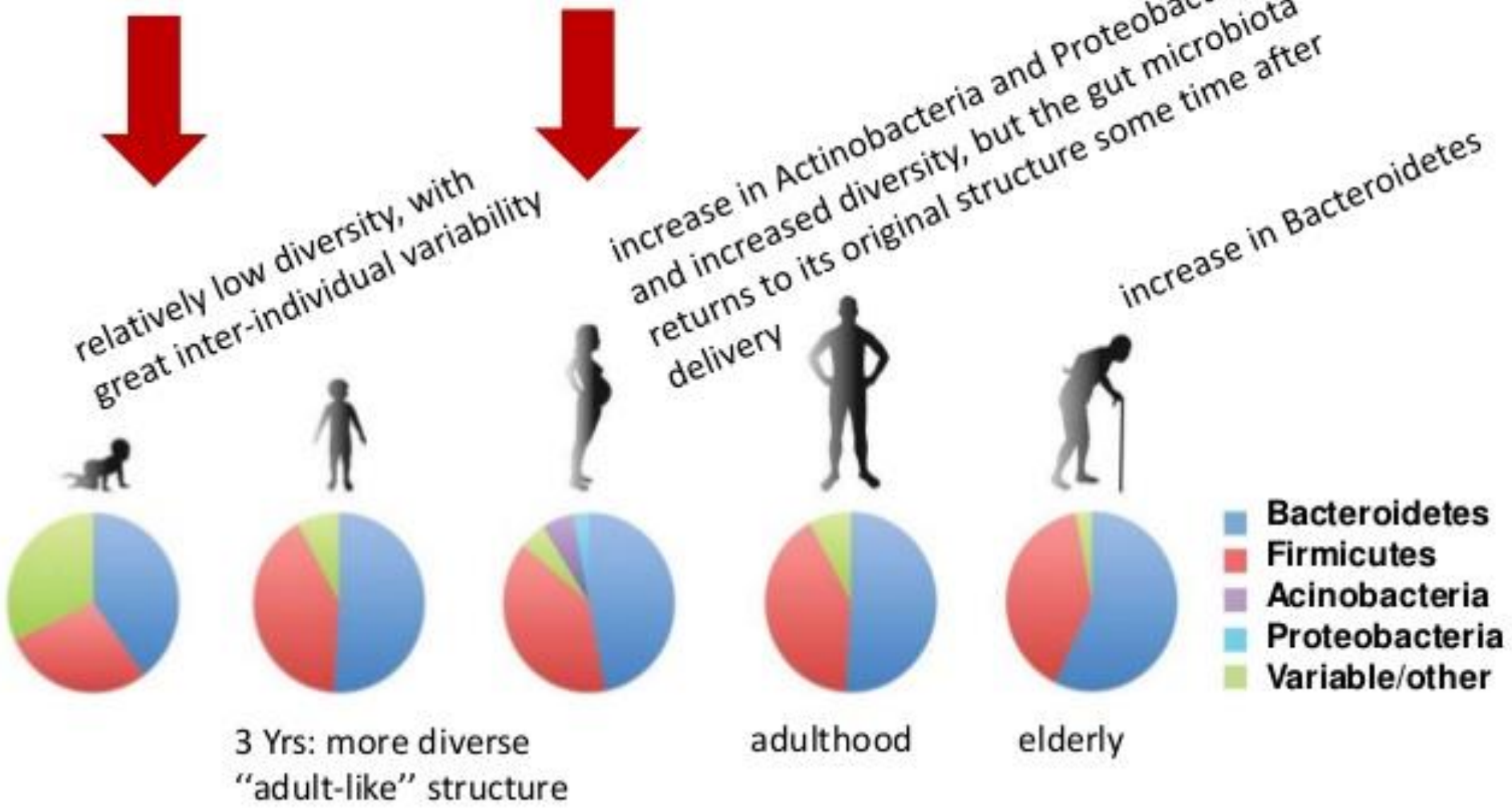


Figure 3. Different distribution of bacterial taxa in children with irritable bowel syndrome was correlated with the relative frequency of abdominal pain.59 Bacterial taxa (specified in leftmost column) were defined by randomForest and confirmed by feature selection using Boruta. The list is sorted first by Mann-Whitney *U* score followed by the largest disparity in medians for each group. Taxa represent the lowest taxonomic depth (Genus) that is labeled by the Ribosomal Database Project Classifier. Red rectangles display the HM (high-medium) abdominal pain phenotype. Light blue rectangles display the L0 LO (low-none) abdominal pain phenotype. *Boxes* represent the first quartile, median and third quartile of the OTU distributions for each pain group. Empty circles represent outliers that are 1.5 greater than the respective interquartile ranges. (A) OTUs with greater abundance in patients with HM vs L0 abdominal pain phenotypes. (B) OTUs with reduced abundance in patients with HM vs L0 abdominal pain phenotypes. Published with permission from Gastroenterology.

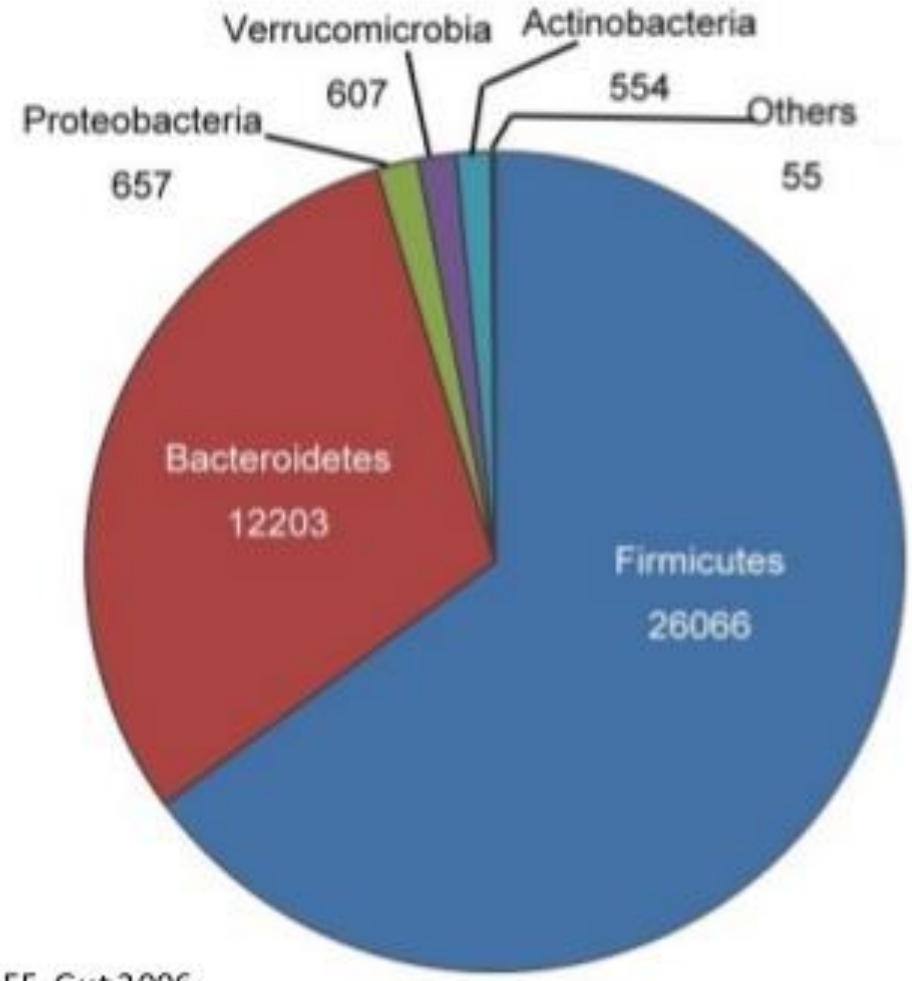
Published in: Delphine M. Saulnier; Yehuda Ringel; Melvin B. Heyman; Jane A. Foster; Premysl Bercik; Robert J. Shulman; James Versalovic; Elena F. Verdu; Ted G. Dinan; Gail Hecht; Francisco Guarner; *Gut Microbes* **2013,** 4, 17-27.
DOI: 10.4161/gmic.22973

Microbiota: a lifetime *dynamics*



Aleksandar D. Kostic, Michael R. Howitt and Wendy S. Garrett; *Genes Dev.* 2013 27: 701-718

HUMAN GUT MICROBIOTA



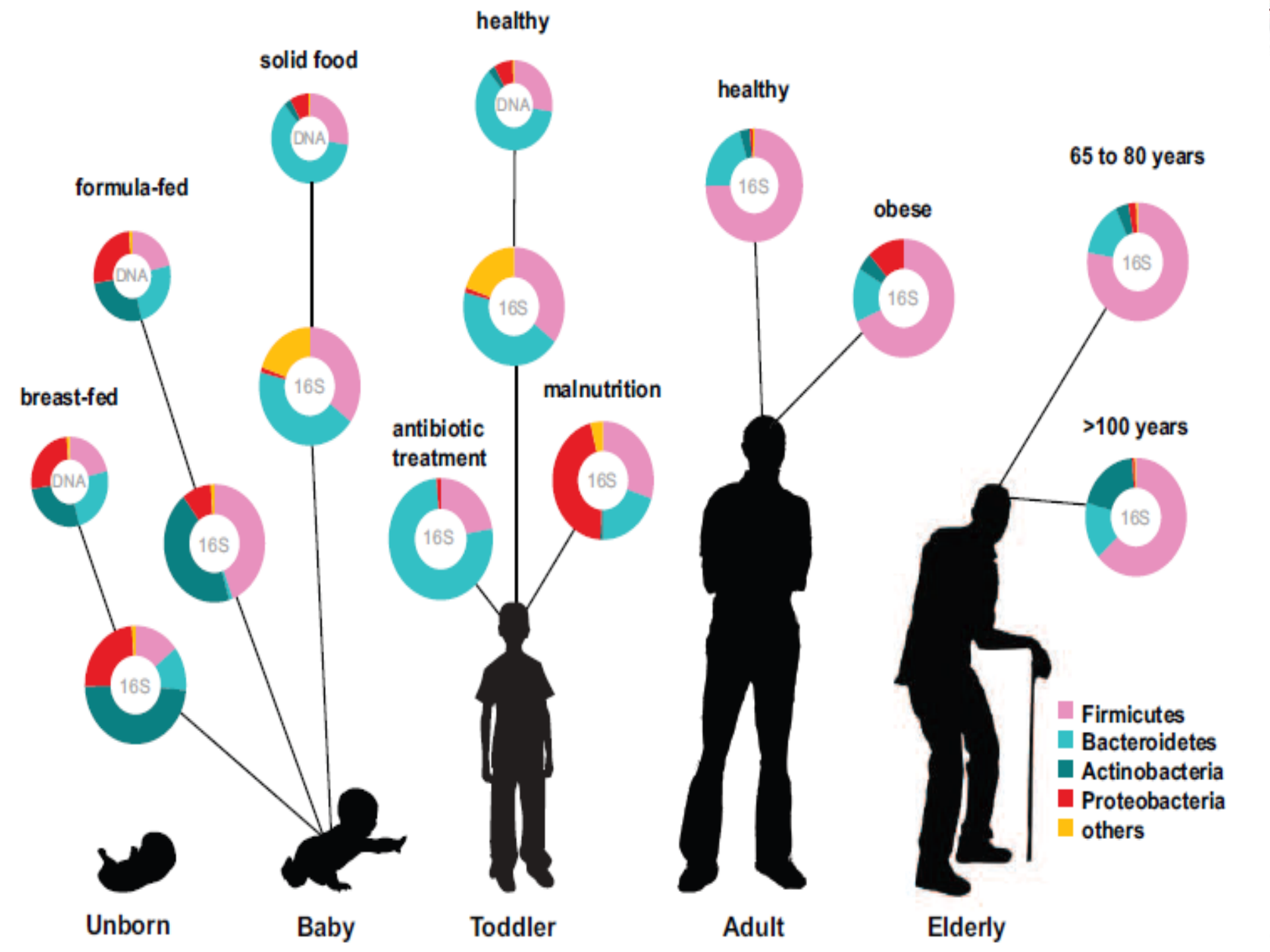
Verdu EF, Gut 2006
Gwee KA, Gut 2003

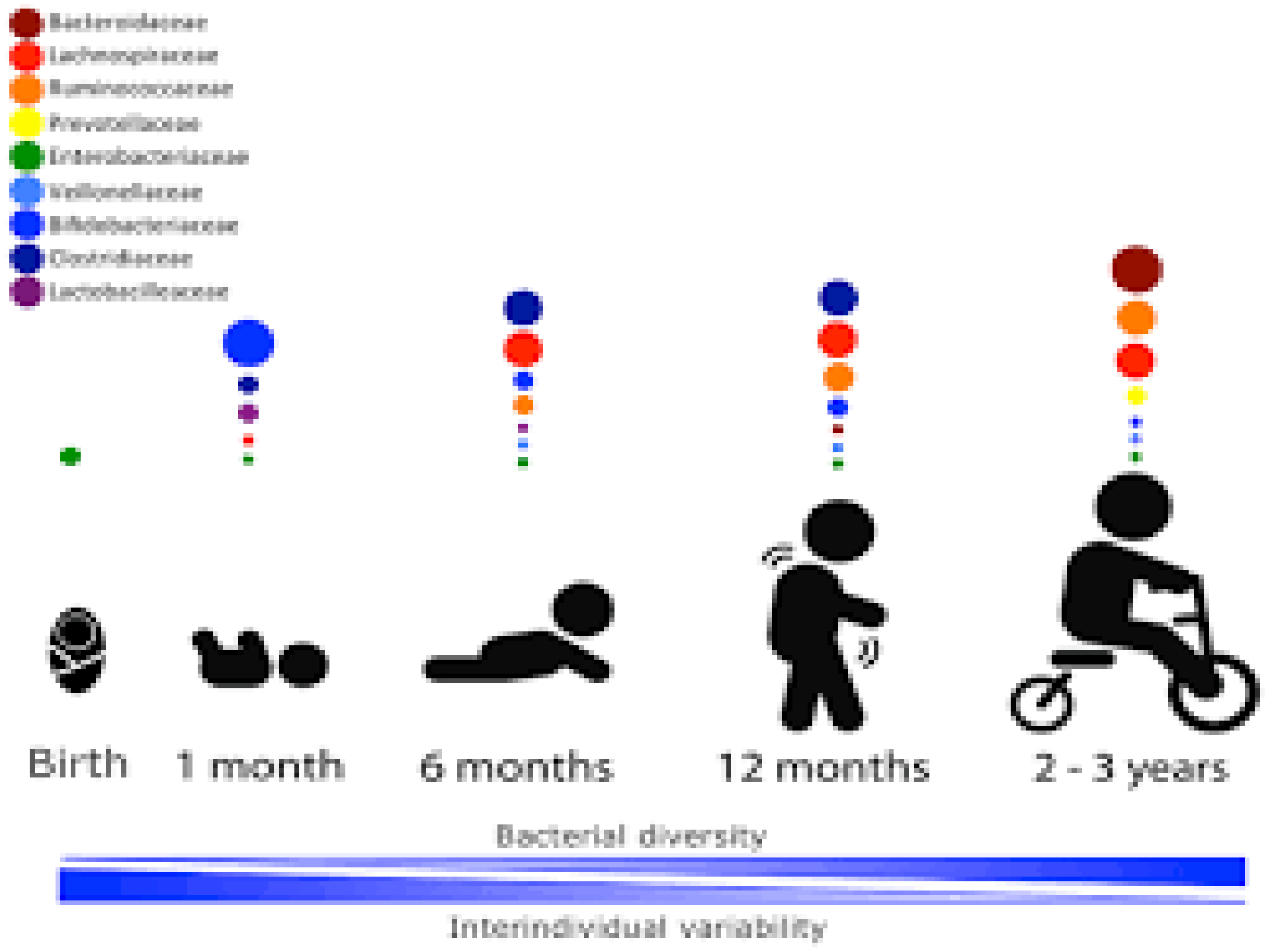
> 90% 2 ceppi dominanti
(*Bacteroidetes*, *Firmicutes*)

< 10% 5 sub-dominanti ceppi
(*Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Cyanobacteria* and *Verrucomicrobia*)

1000-1200 "filotipi"

50-80% Firmicutes dominanti
Clostridium cluster IV e XIVa


healthy
solid food
DNA
formula-fed
DNA
16S
breast-fed
DNA
16S
16S
antibiotic treatment
16S
malnutrition
16S
healthy
16S
obese
16S
65 to 80 years
16S
>100 years
16S
Firmicutes
Bacteroidetes
Actinobacteria
Proteobacteria
others
Unborn
Baby
Toddler
Adult
Elderly

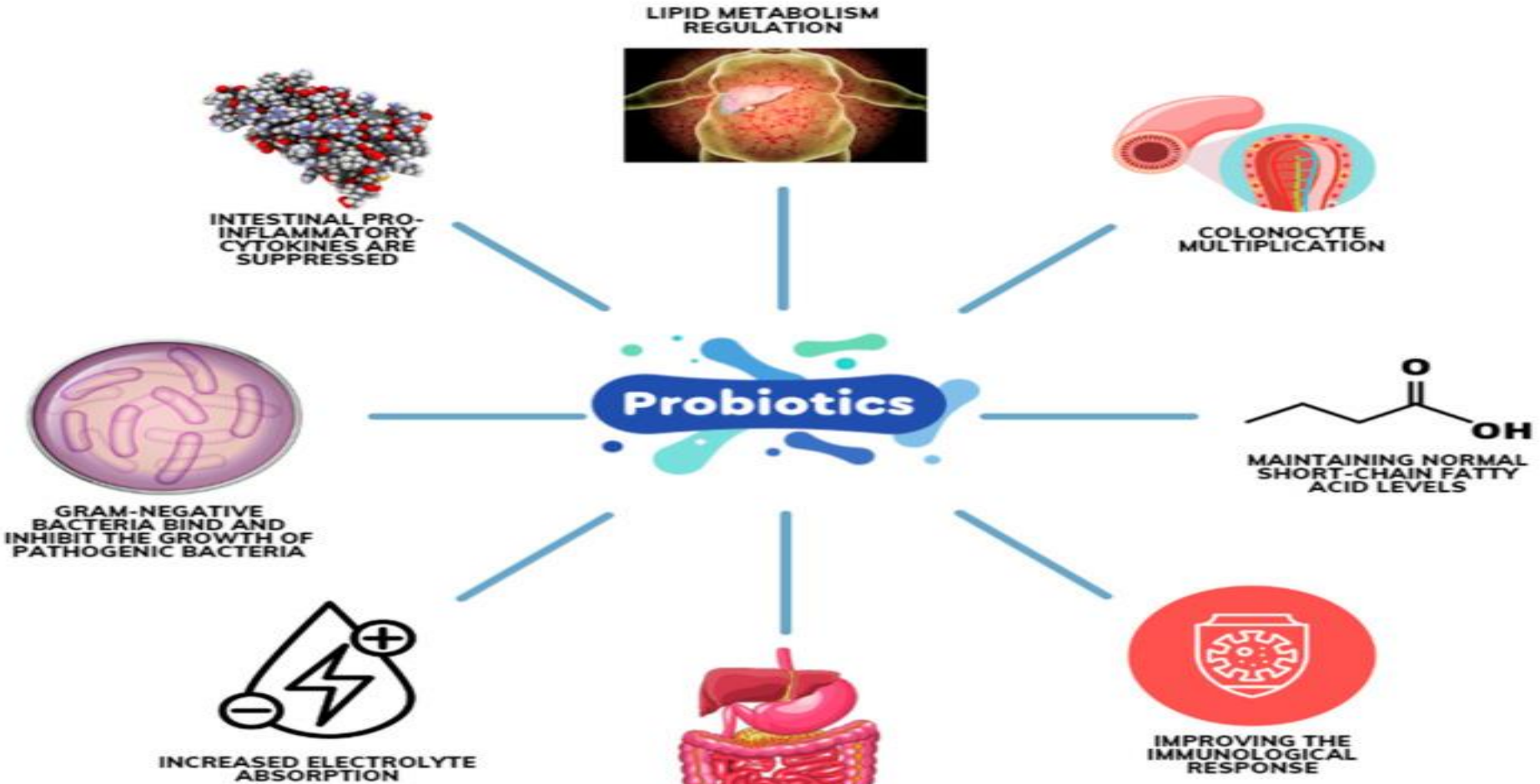

Bacteroidaceae
Lachnospiraceae
Ruminococcaceae
Prevotellaceae
Enterobacteriaceae
Veillonellaceae
Bifidobacteriaceae
Clostridiaceae
Lactobacillaceae
Birth
1 month
6 months
12 months
2 - 3 years
Bacterial diversity
Interindividual variability

Influencing gut microbiota

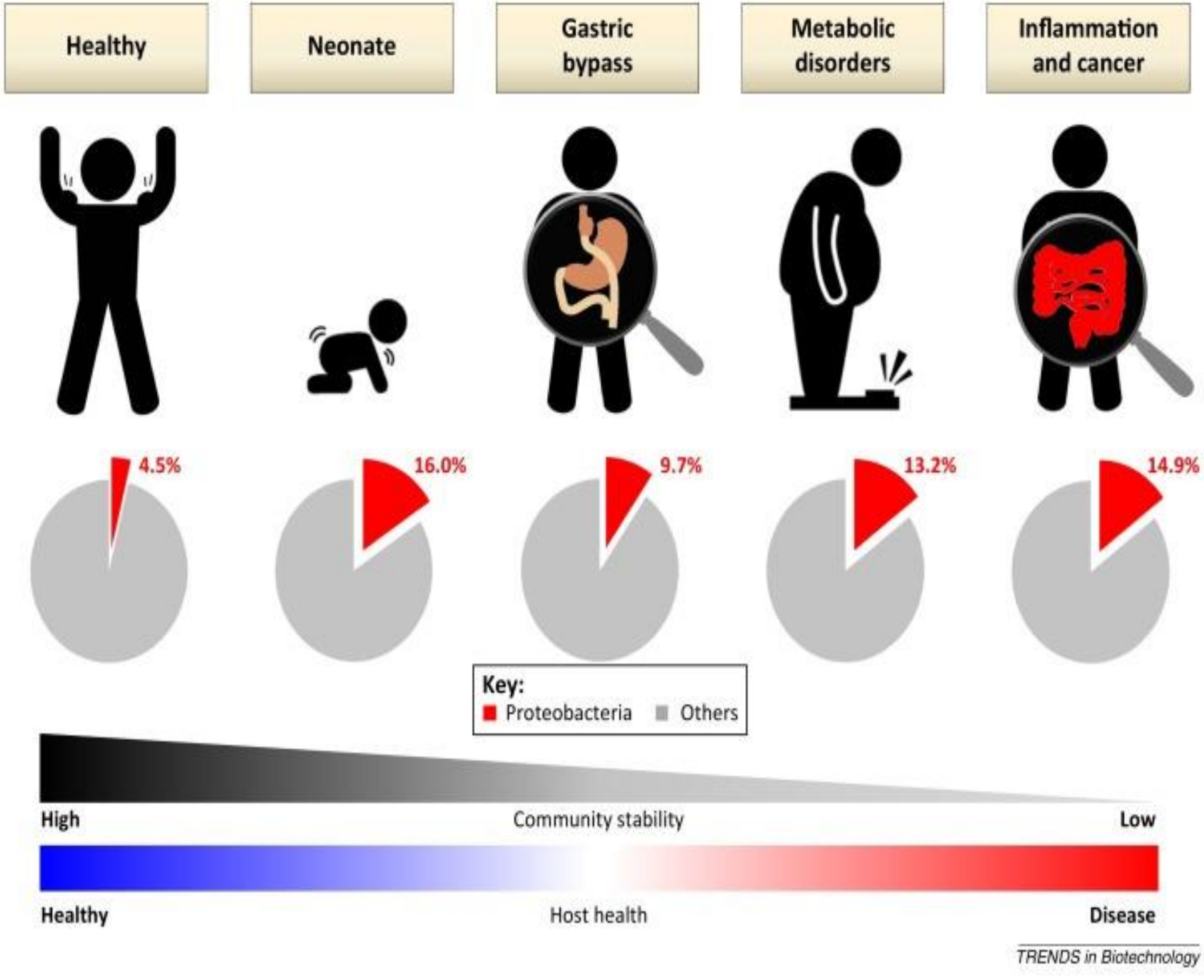
Favor bacteroidetes (leanness)	Favor firmicutes (obesity)
• Maternal well being • Vaginal delivery • Breastfeeding • Less exposure to antibiotics	• Maternal stress • C-section • Formula feeding • More refined carbohydrates • Greater exposure to antibiotics • High fat diet

Christoph Reinhardt, Christopher S. Reigstad, and Fredrik Ba¨ckhed. Journal of Pediatric Gastroenterology and Nutrition. 48:249–256 © 2009

Mehanizam delovanja probiotika

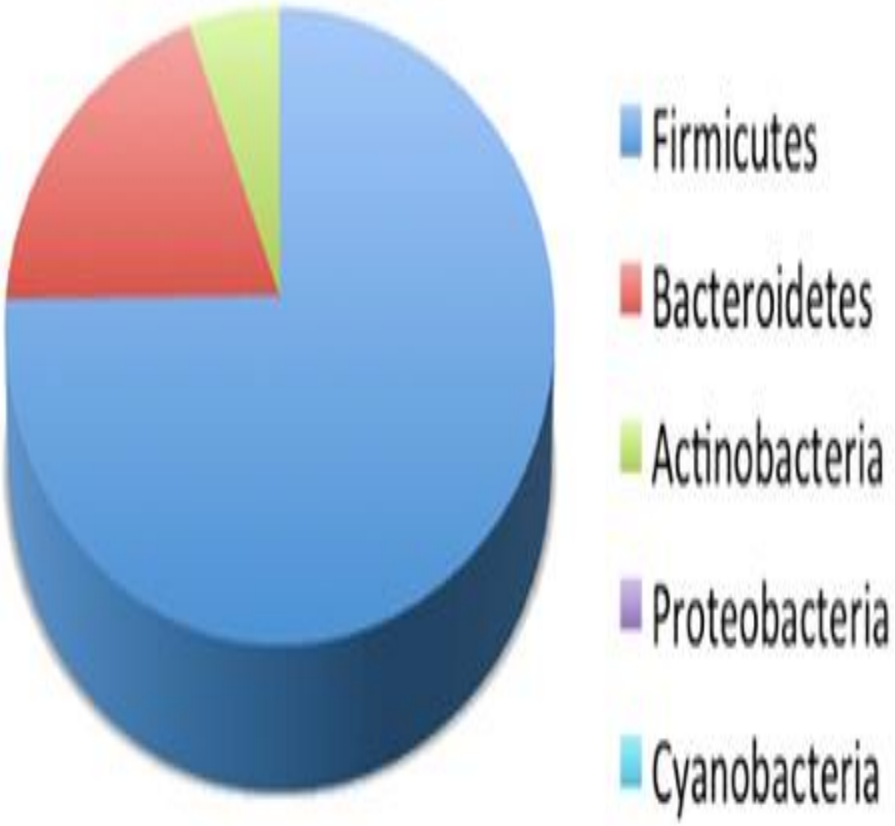


Maftei NM, Raileanu CR, Balta AA, Ambrose L, Boev M, Marin DB, Lisa EL. The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties. Microorganisms. 2024 Jan 23;12(2):234.

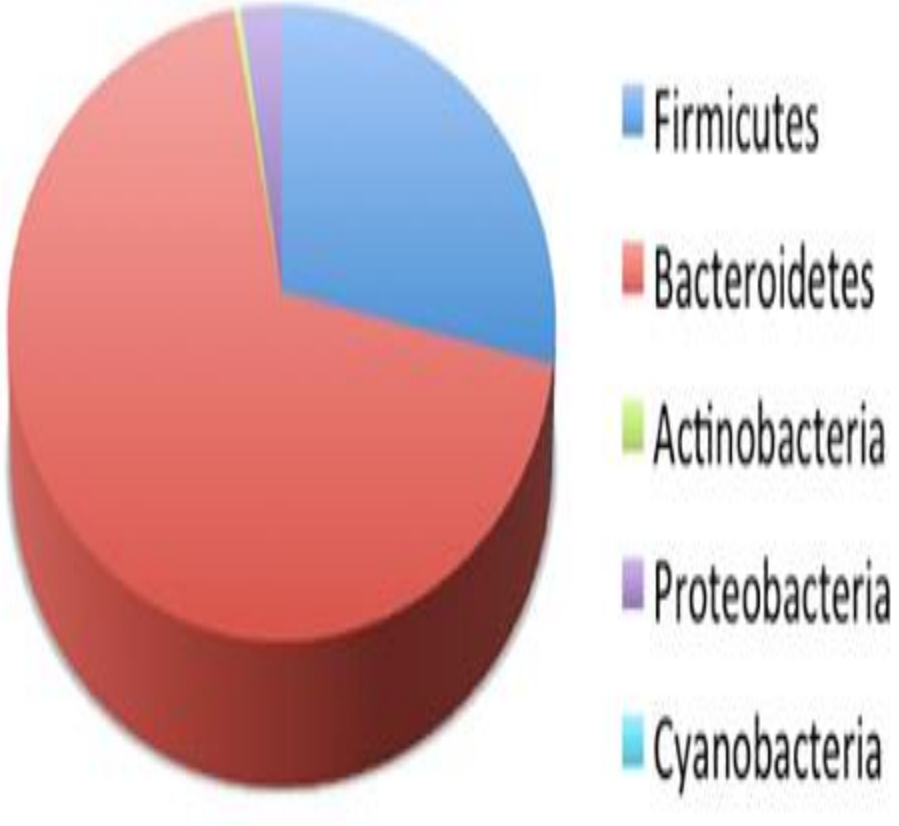


TRENDS in Biotechnology

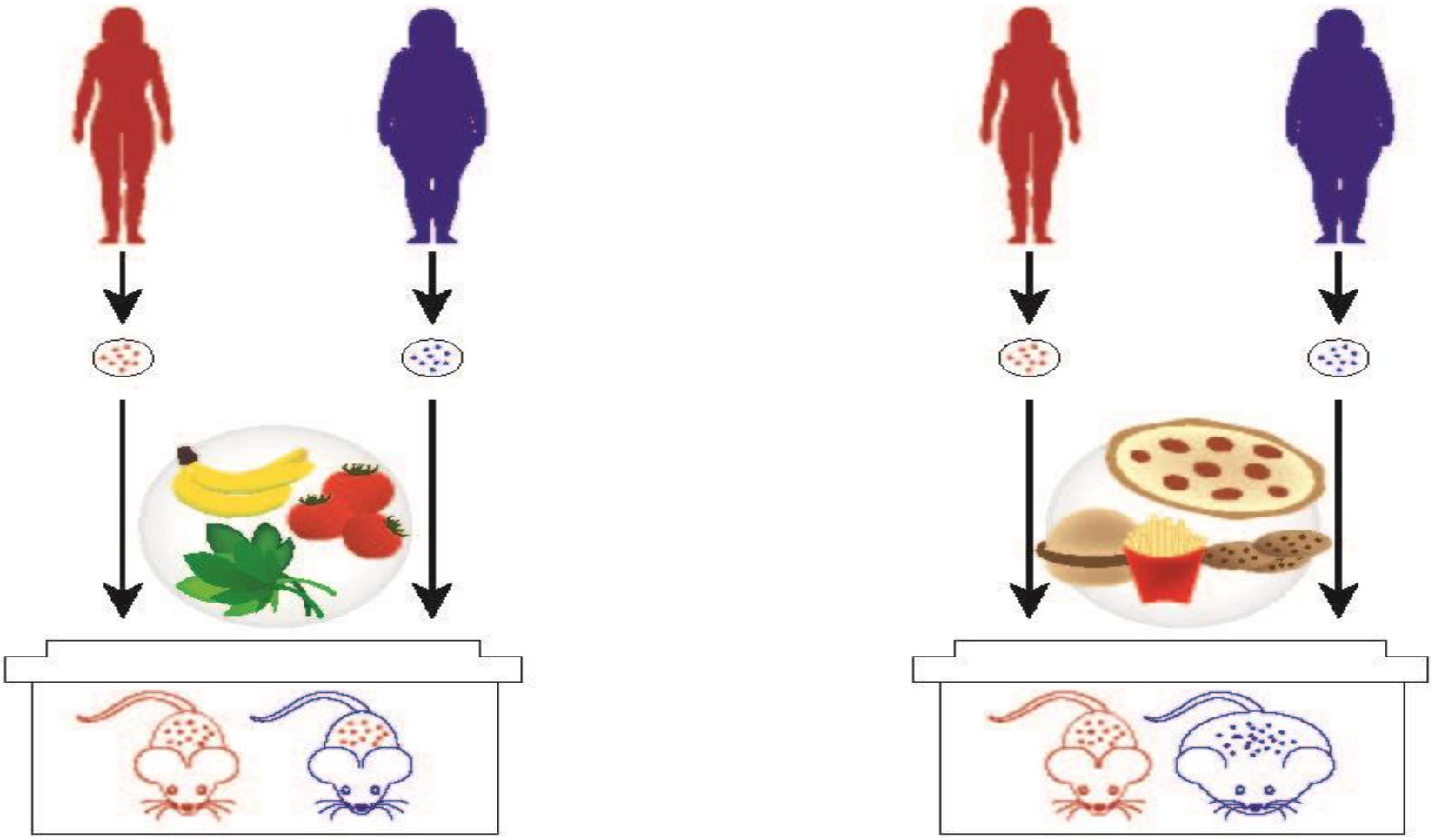
Lots of Meat + Fat + lots & lots of plants / fiber



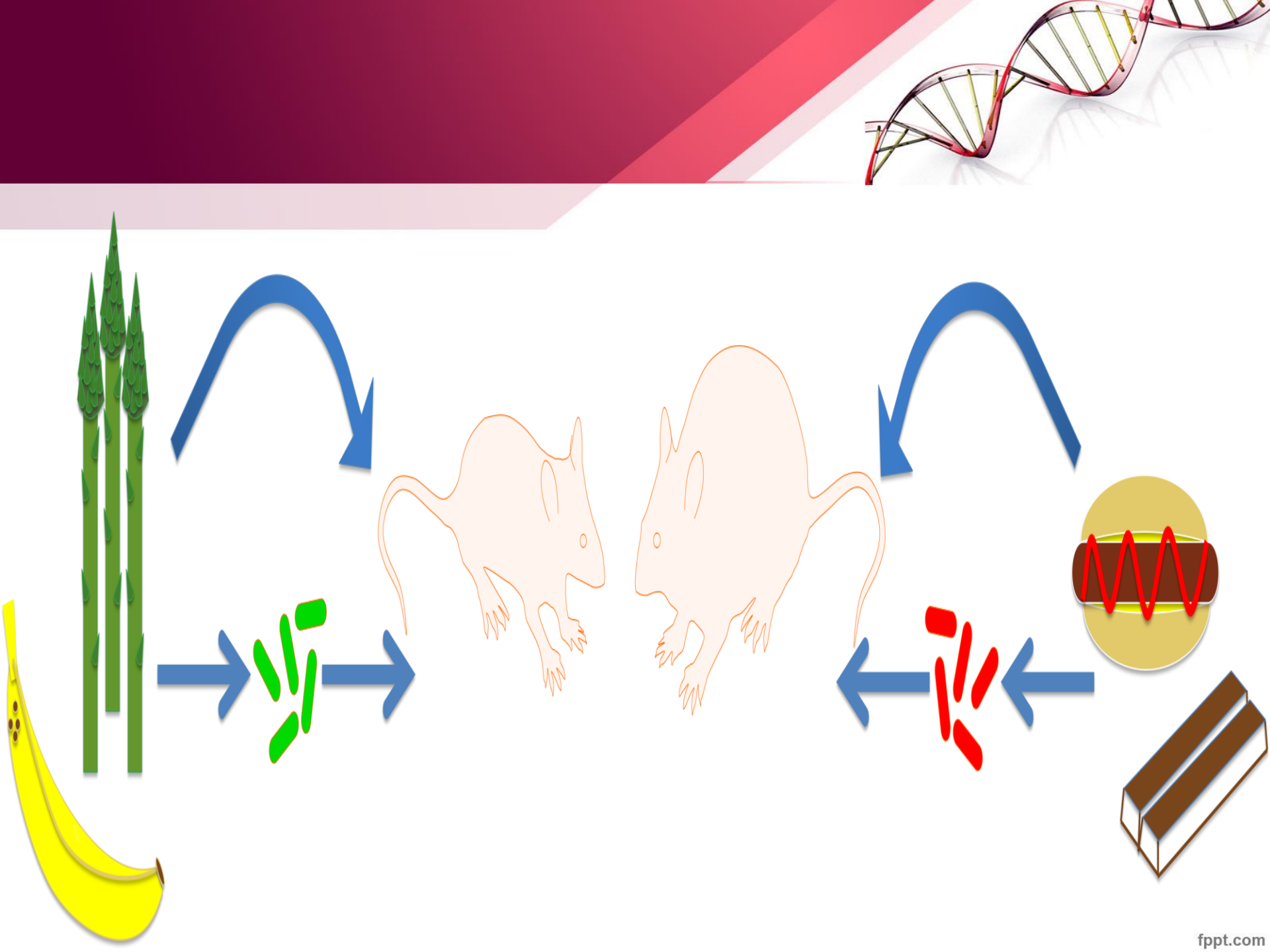
Lots of Meat + Fat + very little plants / fiber

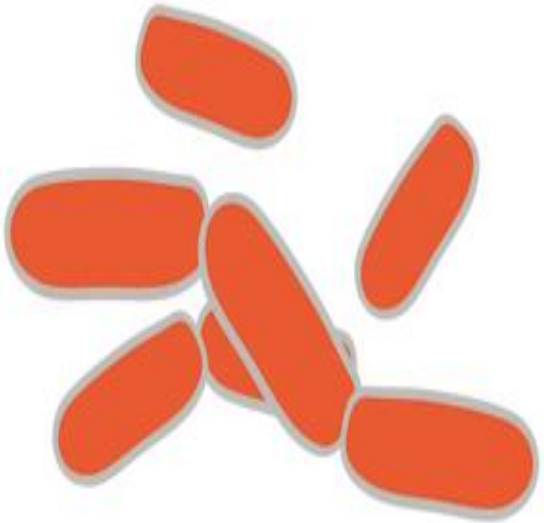


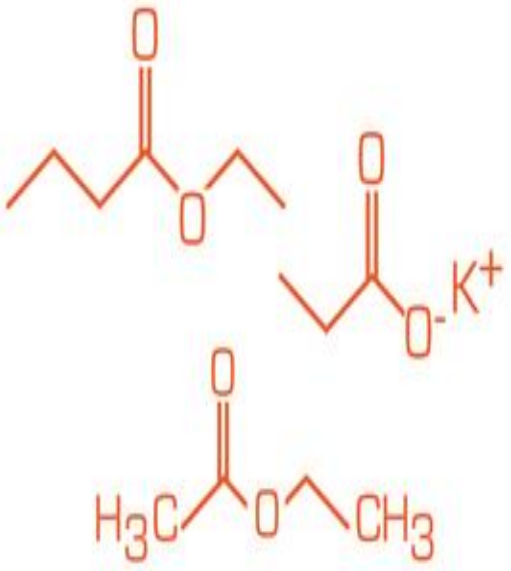
Diet Matters



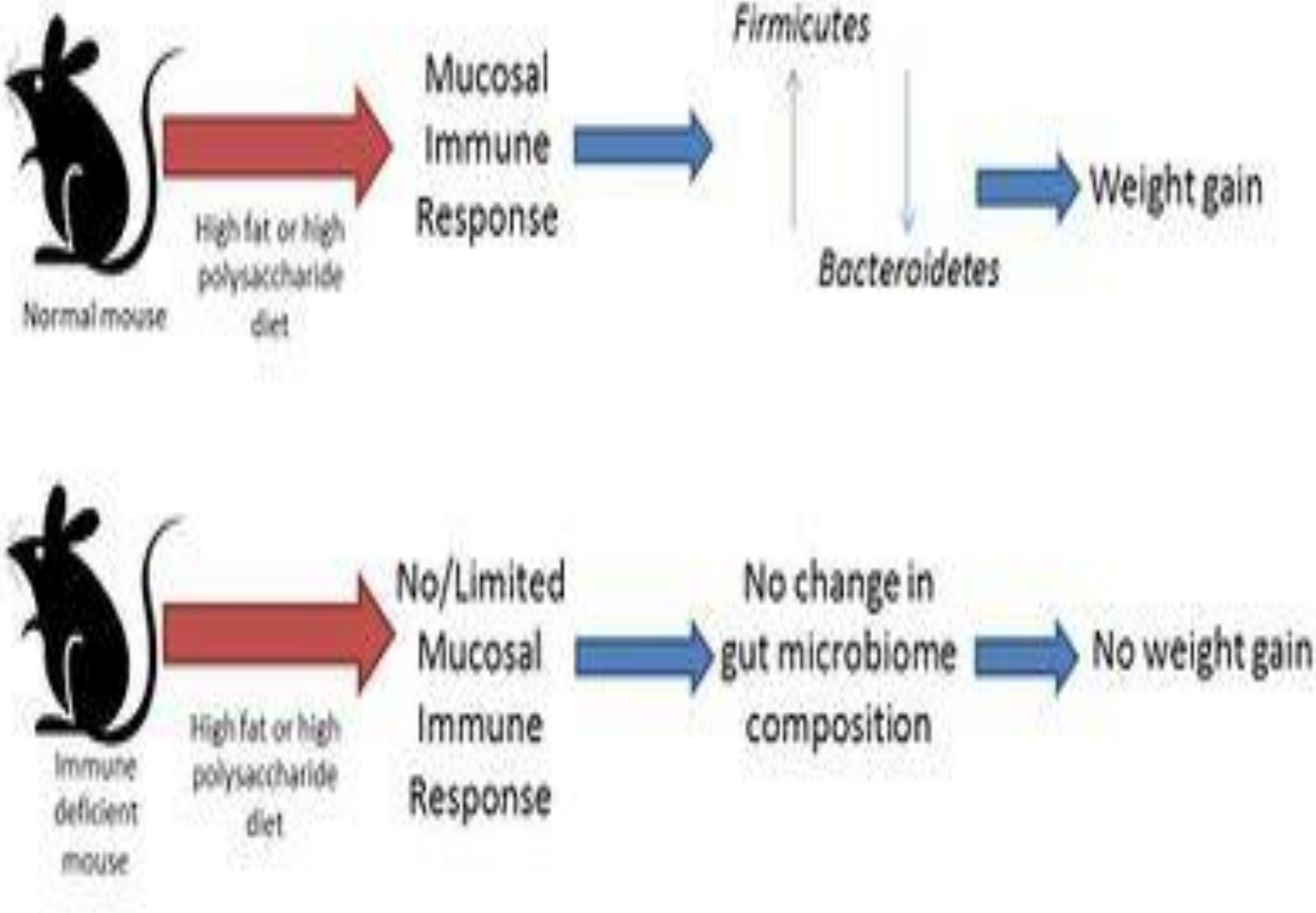
Mice become obese when given microbes from an obese human. But mice stay lean if they get microbes from a lean cage-mate (left). That doesn't happen if the mice eat an unhealthy diet (right).

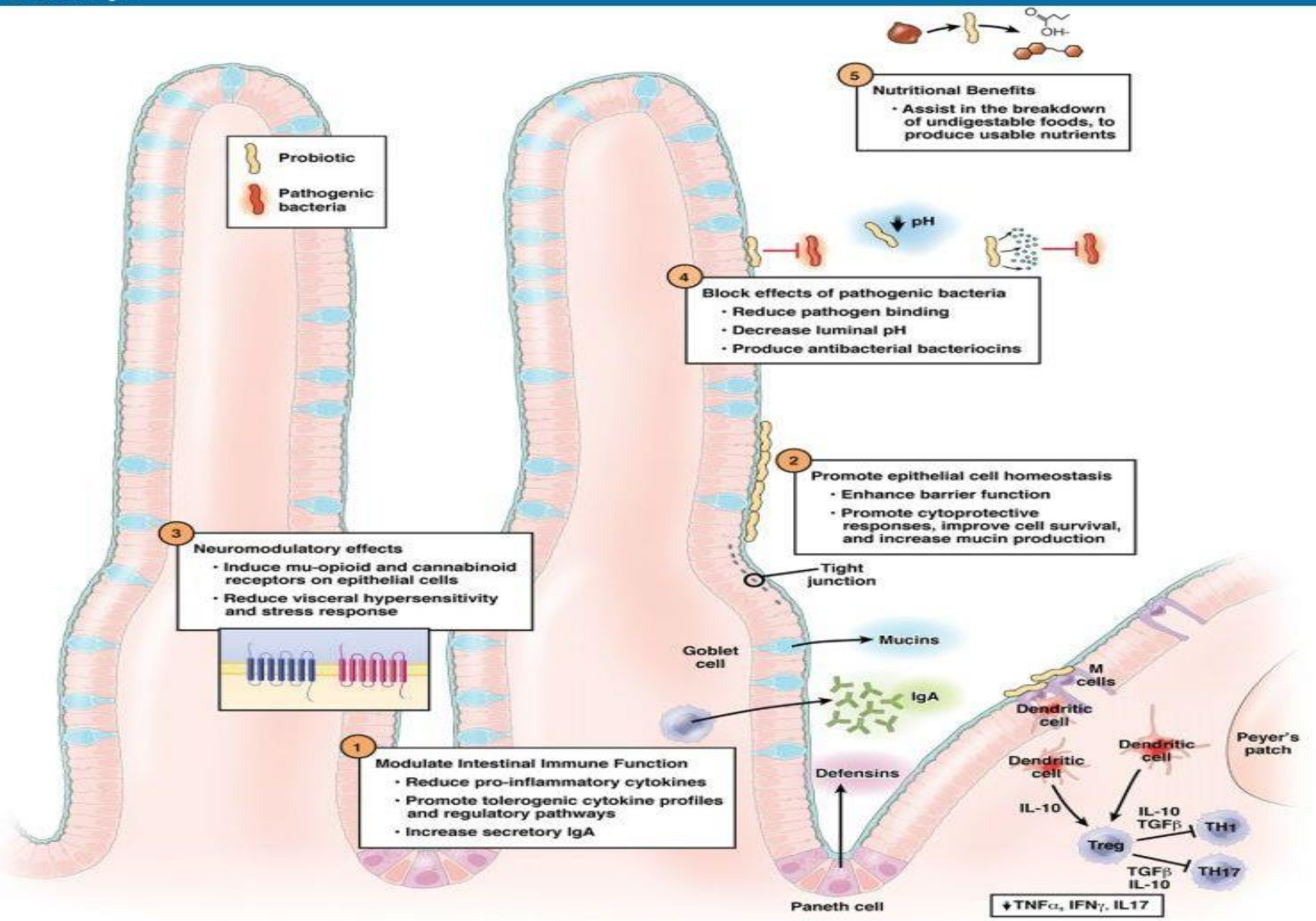


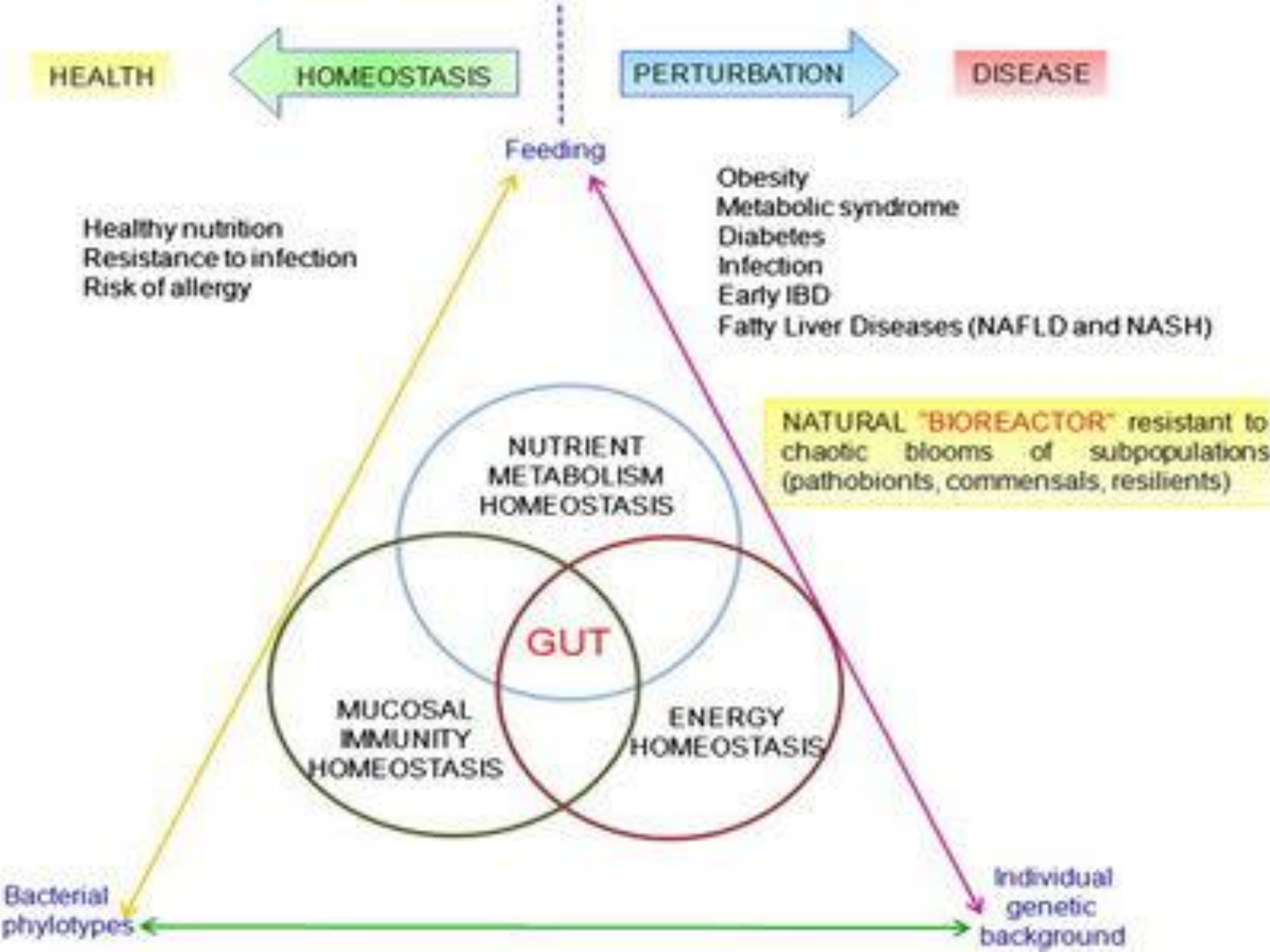


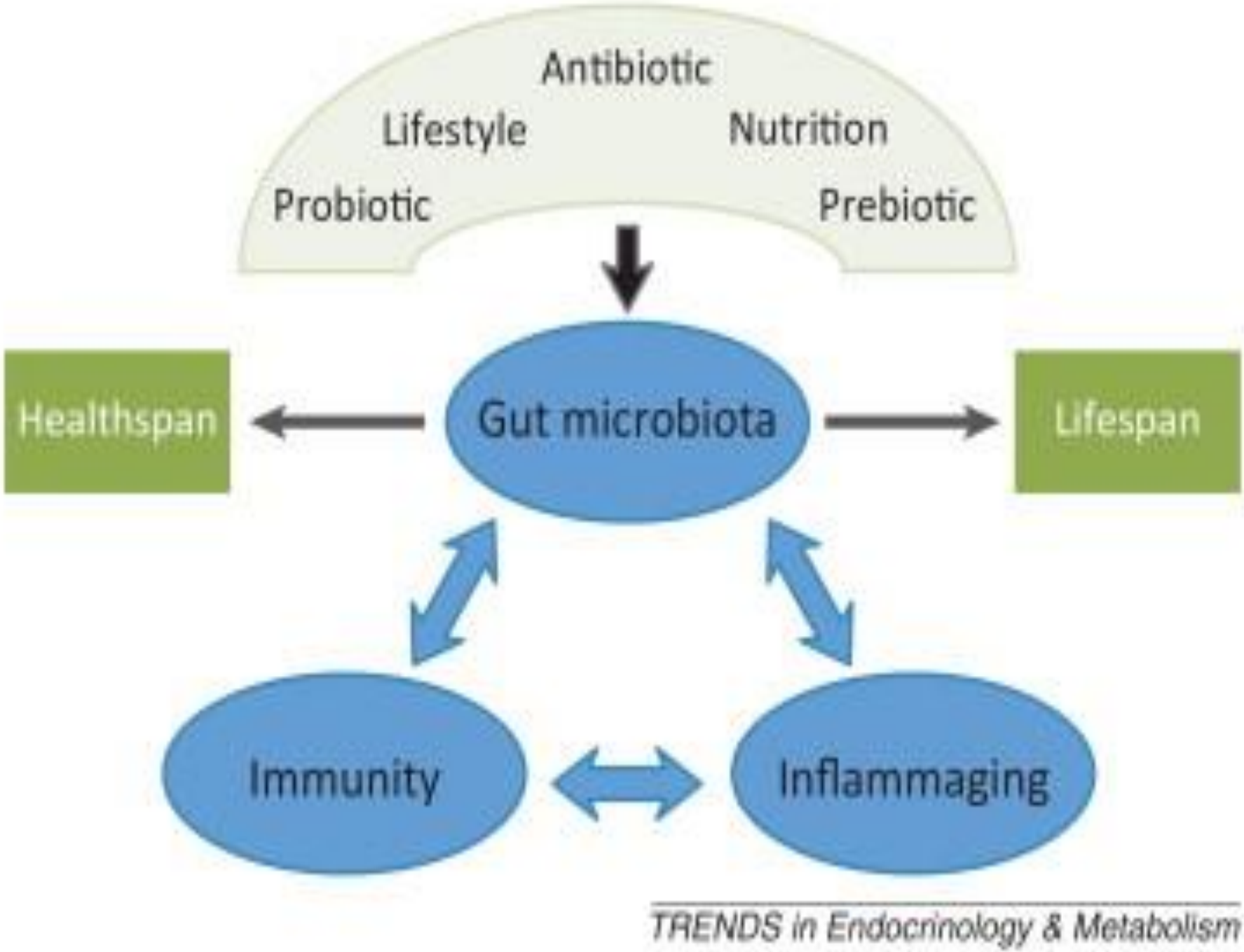


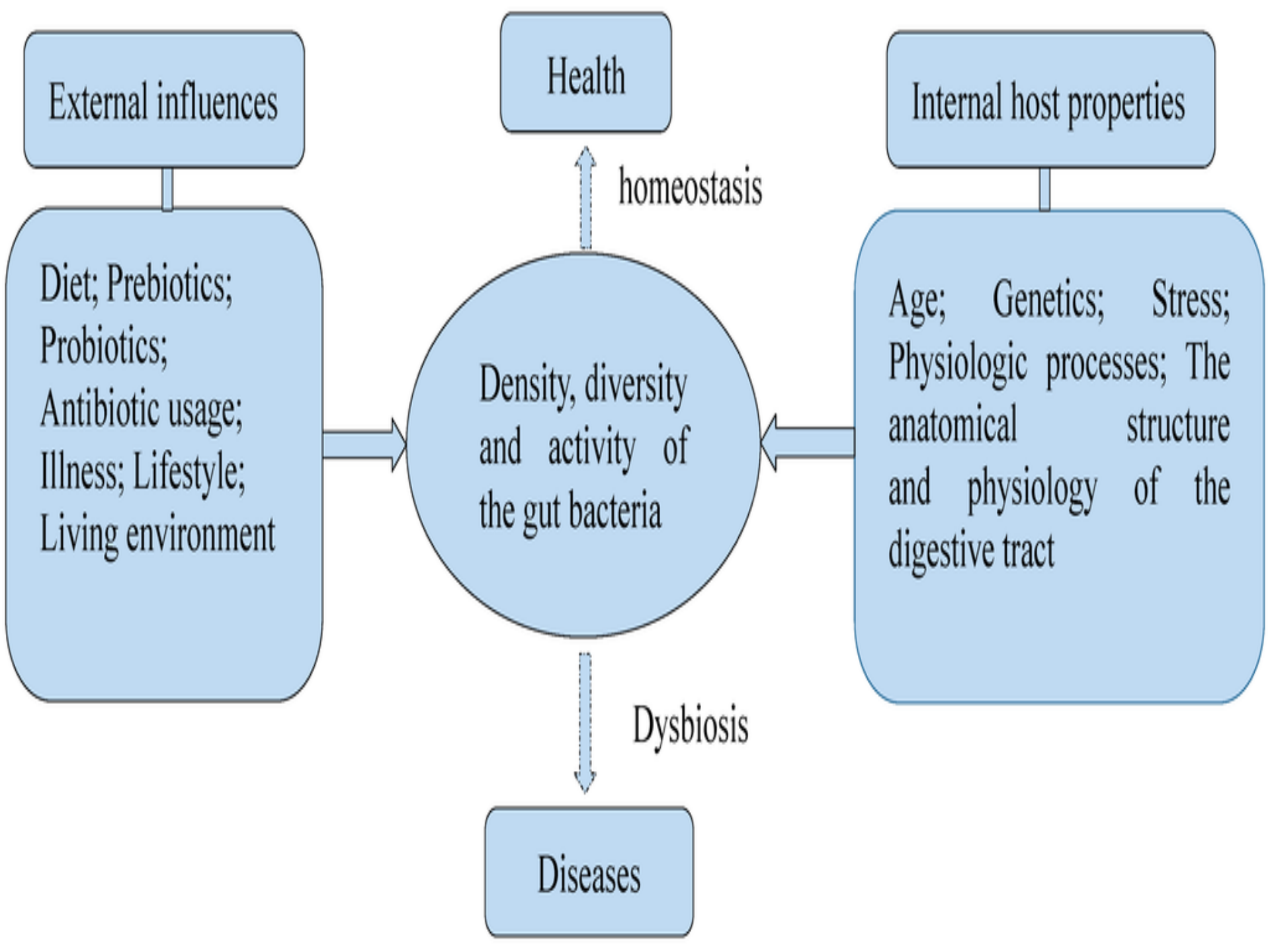
Ingestion of dietary fiber → Fermentation by bacteria → Production of short-chain fatty acids


Normal mouse
High fat or high polysaccharide diet
Mucosal Immune Response
Firmicutes
Bacteroidetes
Weight gain
Immune deficient mouse
High fat or high polysaccharide diet
No/Limited Mucosal Immune Response
No change in gut microbiome composition
No weight gain



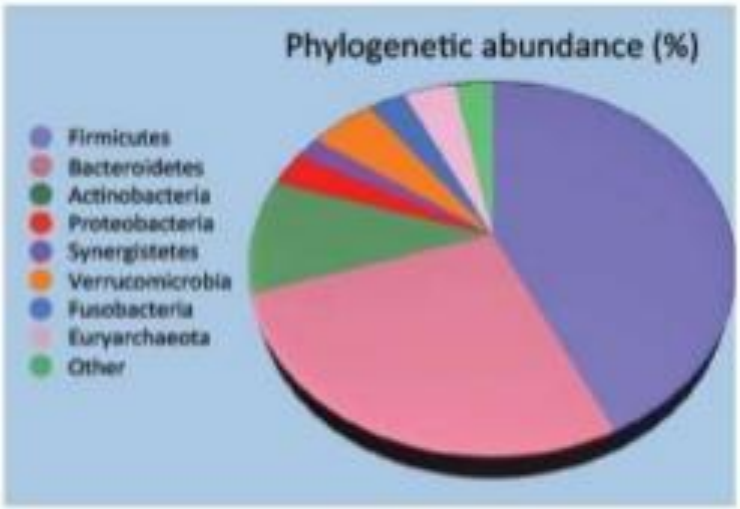

HEALTH
HOMEOSTASIS
PERTURBATION
DISEASE
Feeding
Healthy nutrition
Resistance to infection
Risk of allergy
Obesity
Metabolic syndrome
Diabetes
Infection
Early IBD
Fatty Liver Diseases (NAFLD and NASH)
NATURAL "BIOREACTOR" resistant to chaotic blooms of subpopulations (pathobionts, commensals, resilients)
NUTRIENT METABOLISM HOMEOSTASIS
GUT
MUCOSAL IMMUNITY HOMEOSTASIS
ENERGY HOMEOSTASIS
Bacterial phylotypes
Individual genetic background

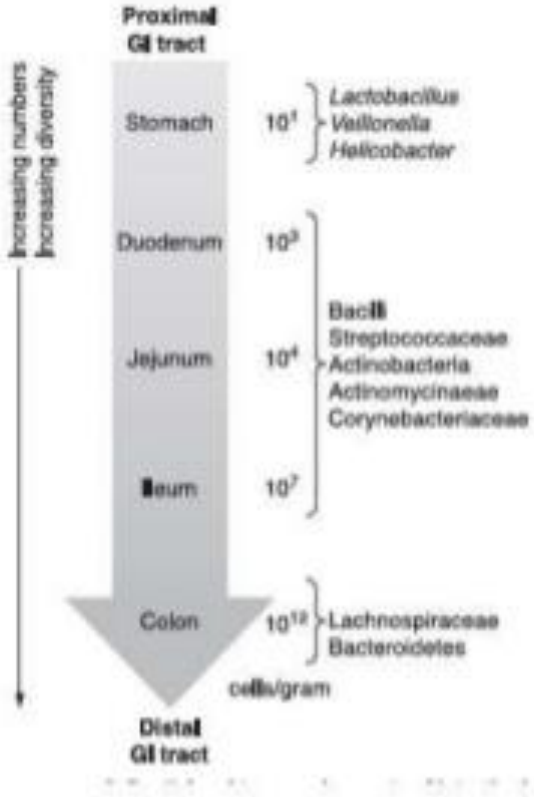

Antibiotic
Lifestyle
Nutrition
Probiotic
Prebiotic
Healthspan
Gut microbiota
Lifespan
Immunity
Inflammaging
TRENDS in Endocrinology & Metabolism

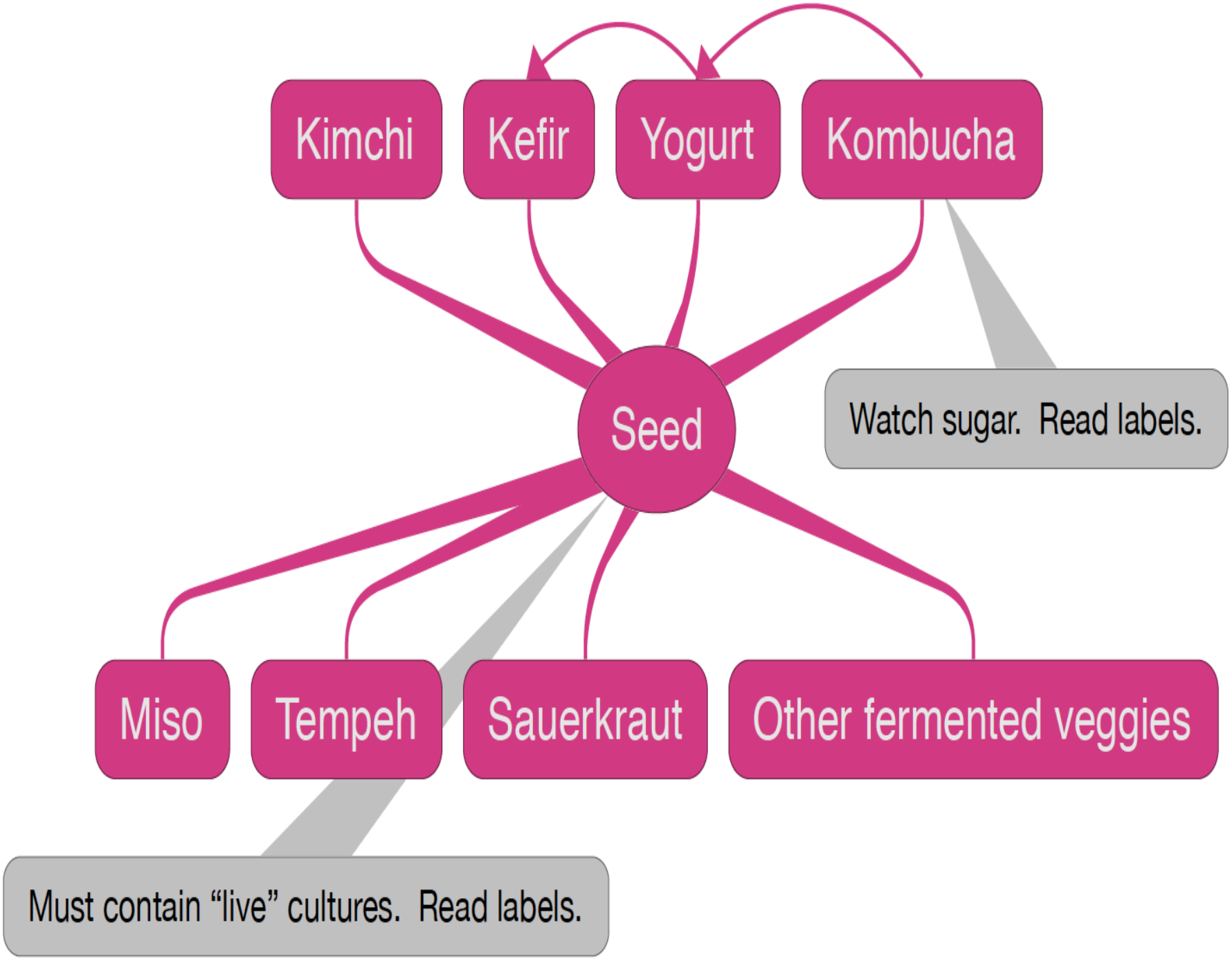

External influences
Health
Internal host properties
homeostasis
Diet; Prebiotics; Probiotics; Antibiotic usage; Illness; Lifestyle; Living environment
Density, diversity and activity of the gut bacteria
Age; Genetics; Stress; Physiologic processes; The anatomical structure and physiology of the digestive tract
Dysbiosis
Diseases

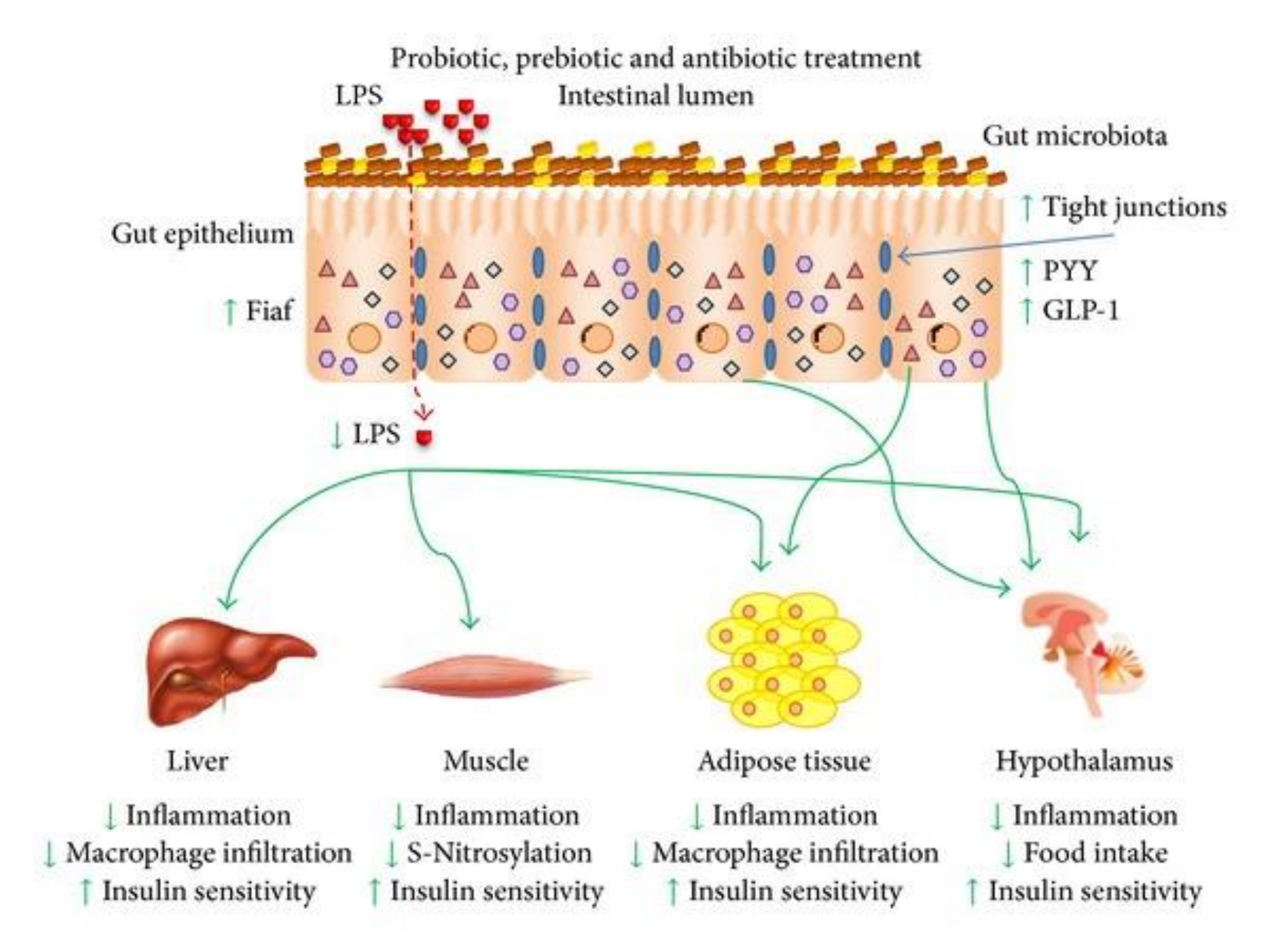
Gut Microbiota: Who is there?

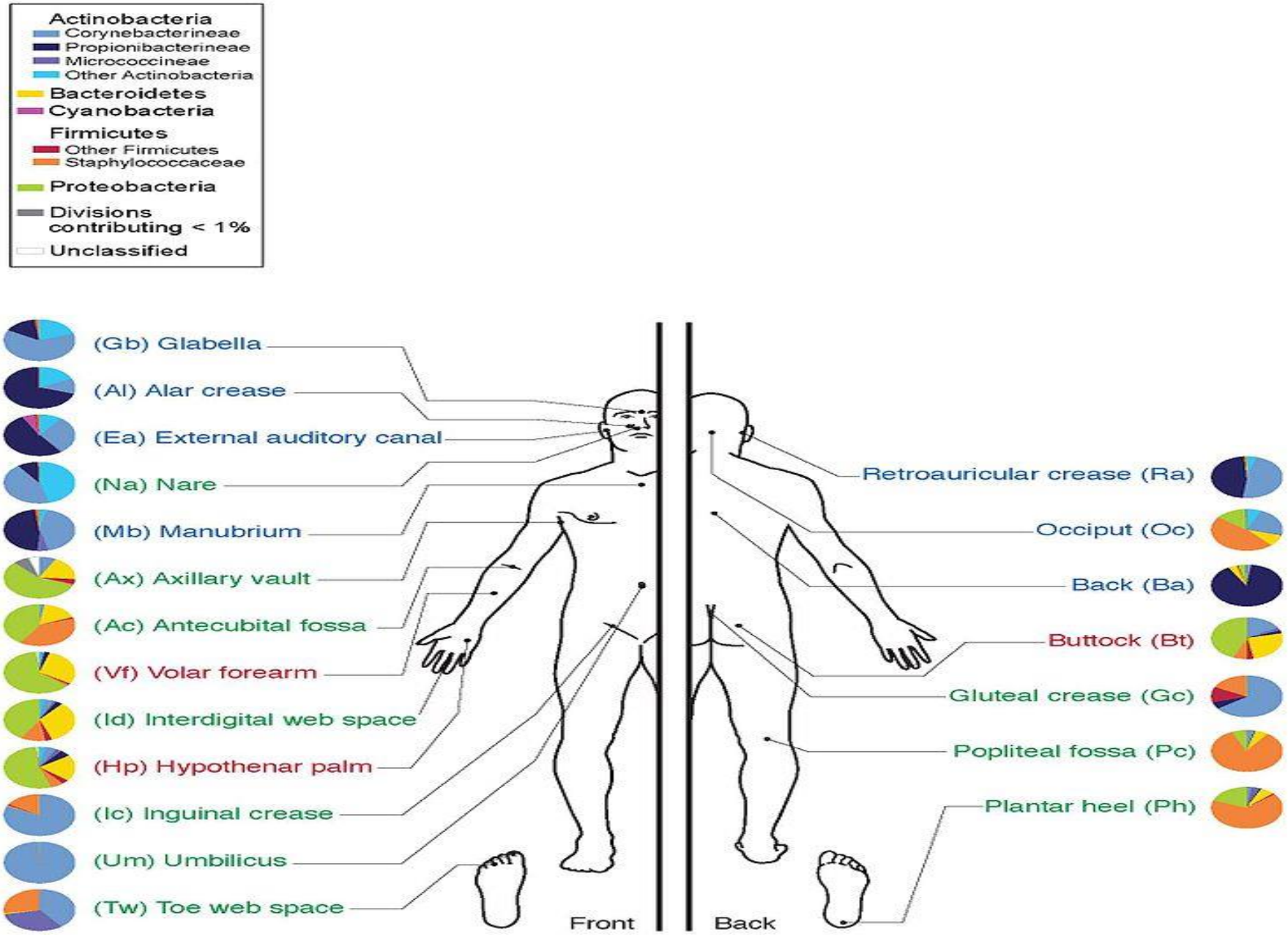
- All mucosal surfaces are colonised with bacteria
- The intestine is a preferred site – over 70% of all bacteria are found in the colon
  - large organ
  - rich in nutrients
- Longitudinal: bacteria increase in number and composition changes from proximal to distal GI tract

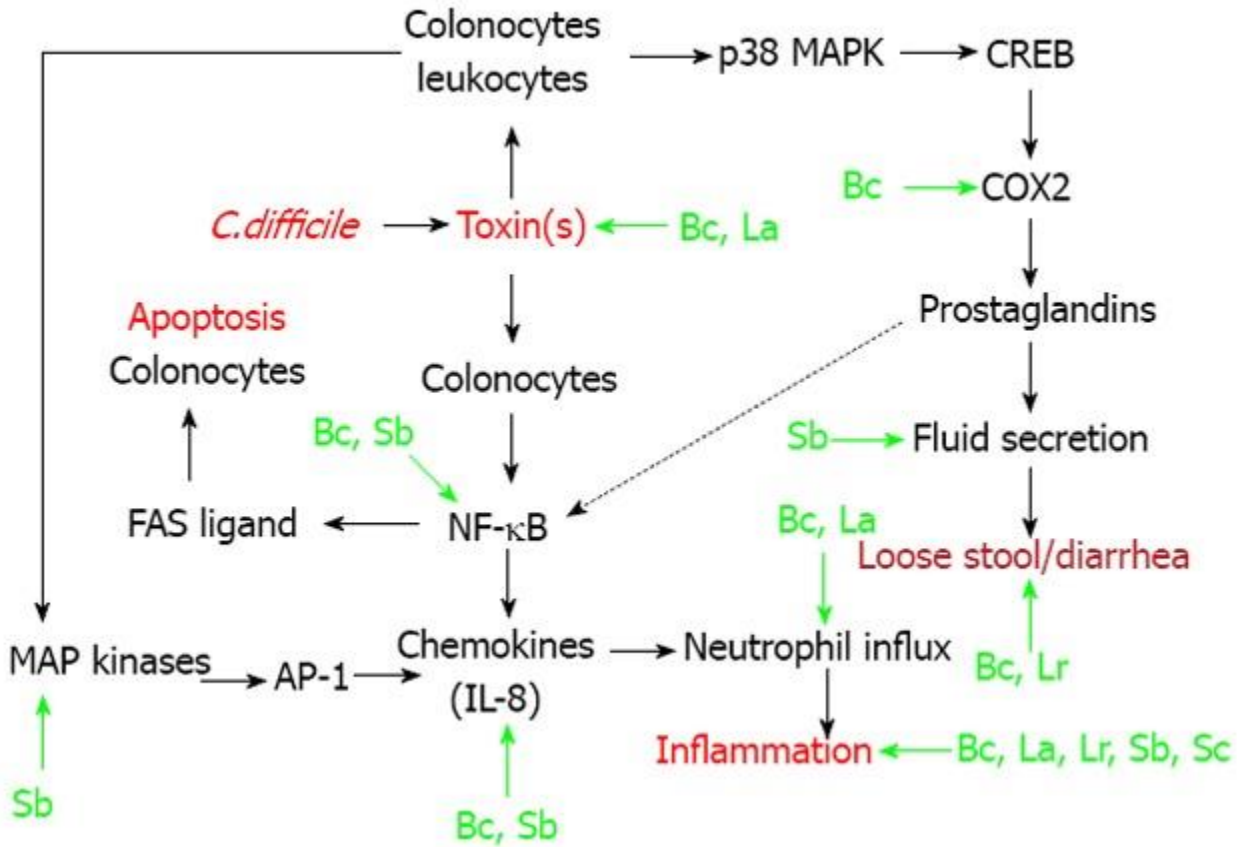




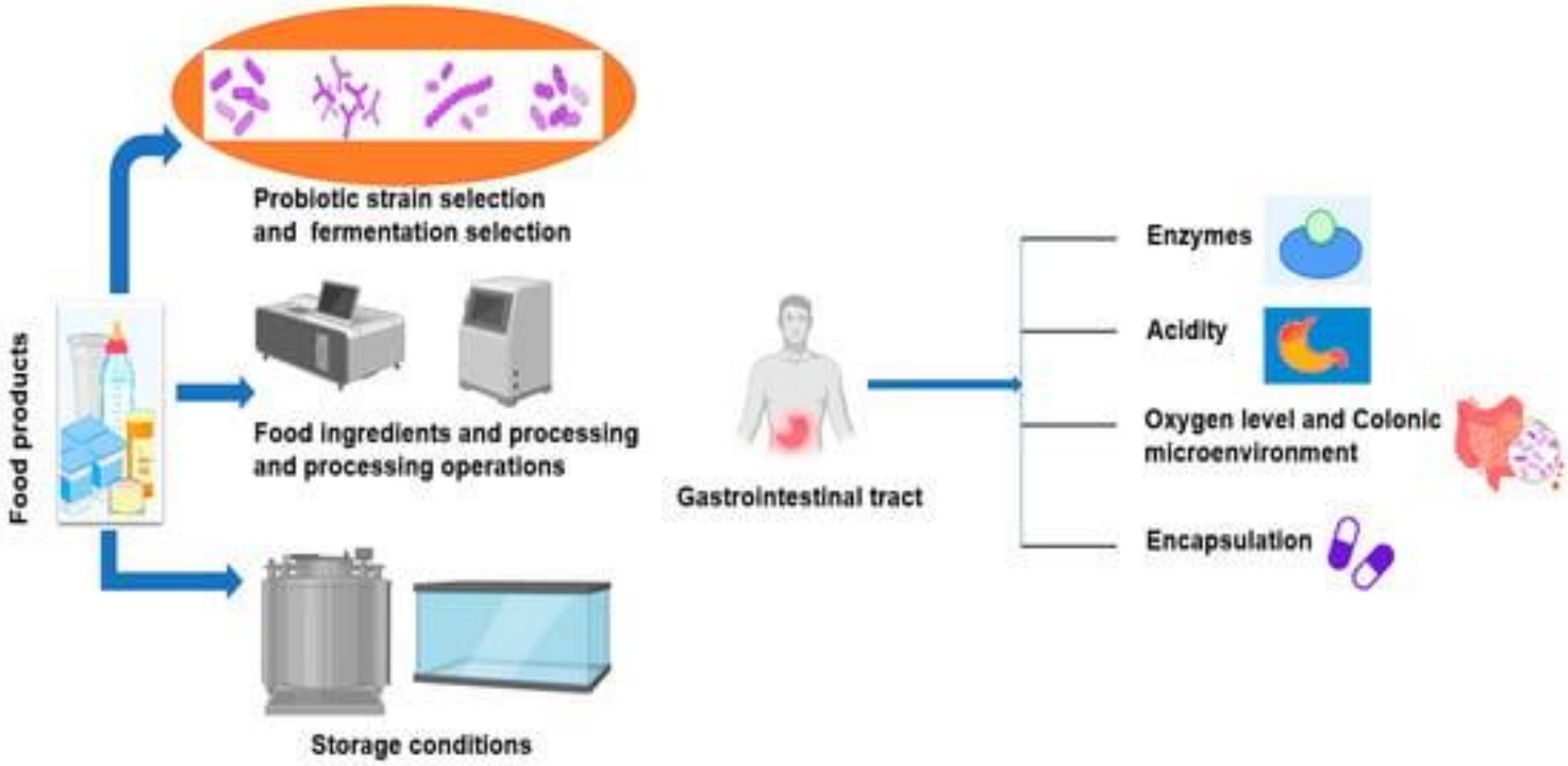

Kimchi
Kefir
Yogurt
Kombucha
Seed
Watch sugar. Read labels.
Miso
Tempeh
Sauerkraut
Other fermented veggies
Must contain “live” cultures. Read labels.


Probiotic, prebiotic and antibiotic treatment
LPS
Intestinal lumen
Gut microbiota
↑ Tight junctions
Gut epithelium
↑ PYY
↑ Fiaf
↑ GLP-1
↓ LPS
Liver
Muscle
Adipose tissue
Hypothalamus
↓ Inflammation
↓ Macrophage infiltration
↑ Insulin sensitivity
↓ Inflammation
↓ S-Nitrosylation
↑ Insulin sensitivity
↓ Inflammation
↓ Macrophage infiltration
↑ Insulin sensitivity
↓ Inflammation
↓ Food intake
↑ Insulin sensitivity


Actinobacteria
Corynebacterineae
Propionibacterineae
Micrococcineae
Other Actinobacteria
Bacteroidetes
Cyanobacteria
Firmicutes
Other Firmicutes
Staphylococcaceae
Proteobacteria
Divisions contributing < 1%
Unclassified
(Gb) Glabella
(Al) Alar crease
(Ea) External auditory canal
(Na) Nare
(Mb) Manubrium
(Ax) Axillary vault
(Ac) Antecubital fossa
(Vf) Volar forearm
(Id) Interdigital web space
(Hp) Hypothenar palm
(Ic) Inguinal crease
(Um) Umbilicus
(Tw) Toe web space
Retroauricular crease (Ra)
Occiput (Oc)
Back (Ba)
Buttock (Bt)
Gluteal crease (Gc)
Popliteal fossa (Pc)
Plantar heel (Ph)
Front
Back

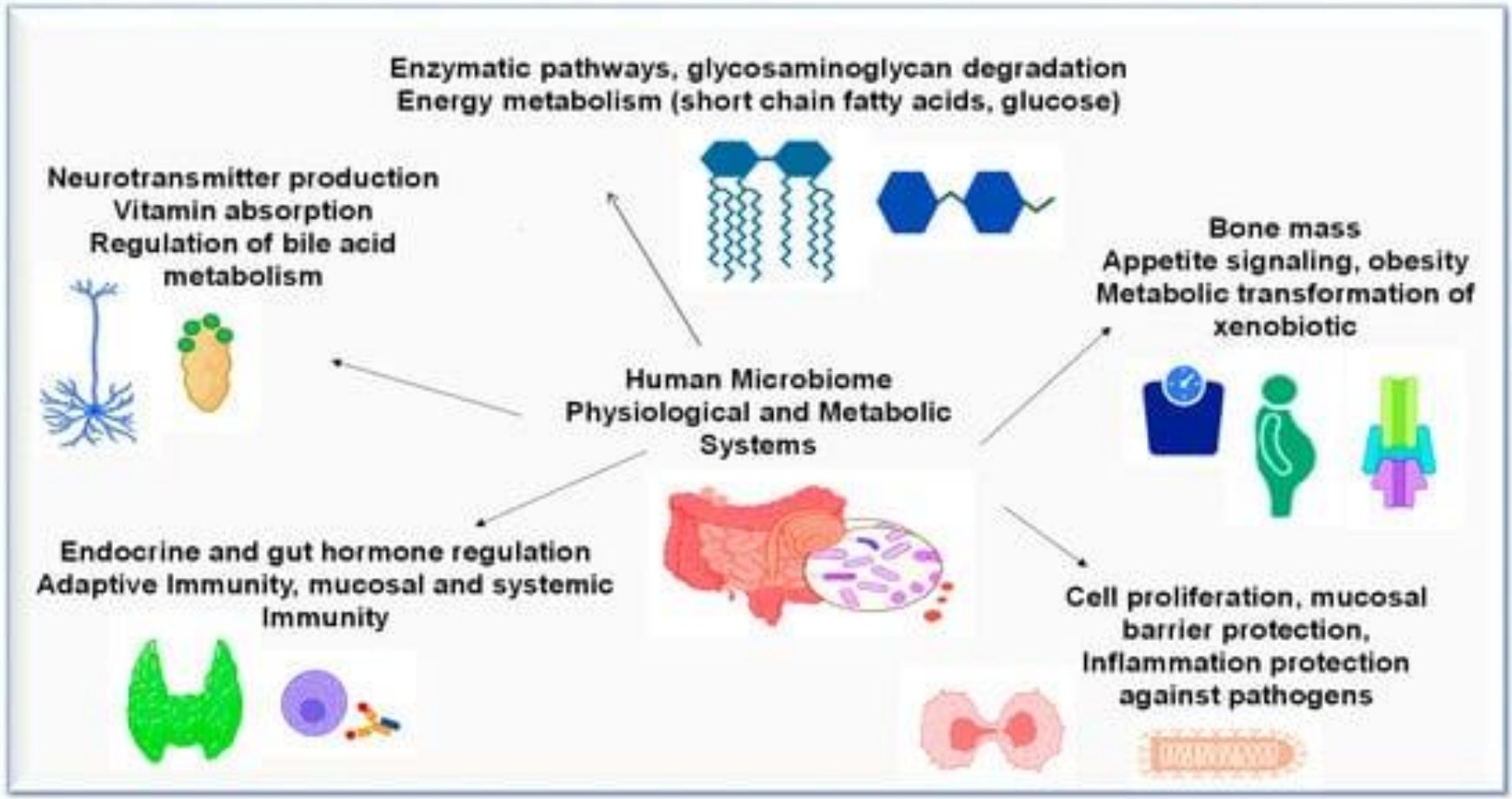

Colonocytes
leukocytes
p38 MAPK
CREB
Bc
COX2
C.difficile
Toxin(s)
Bc, La
Prostaglandins
Apoptosis
Colonocytes
Colonocytes
Bc, Sb
Sb
Fluid secretion
FAS ligand
NF-κB
Bc, La
Loose stool/diarrhea
MAP kinases
AP-1
Chemokines
(IL-8)
Neutrophil influx
Bc, Lr
Inflammation
Bc, La, Lr, Sb, Sc
Sb
Bc, Sb

Faktori koji utiču na održivost probiotika u hrani i gastrointestinalnom sistemu.



Venkatesh GP, Kuruvalli G, Syed K, Reddy VD. An Updated Review on Probiotic Production and Applications. Gastroenterology Insights. 2024; 15(1):221-236.

Fiziološki i metabolički procesi u ljudskom mikrobiomu



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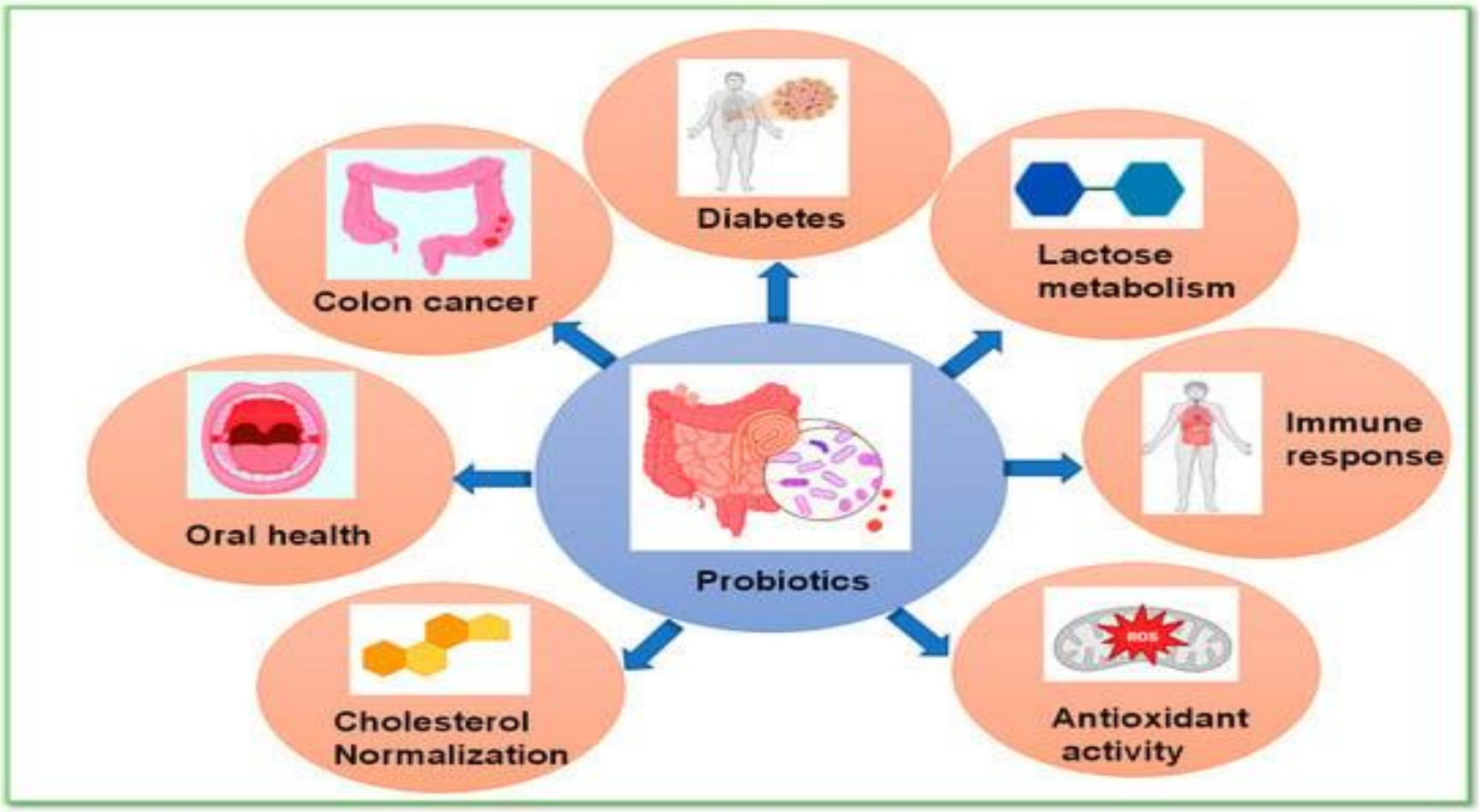
Klinička primena probiotika



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