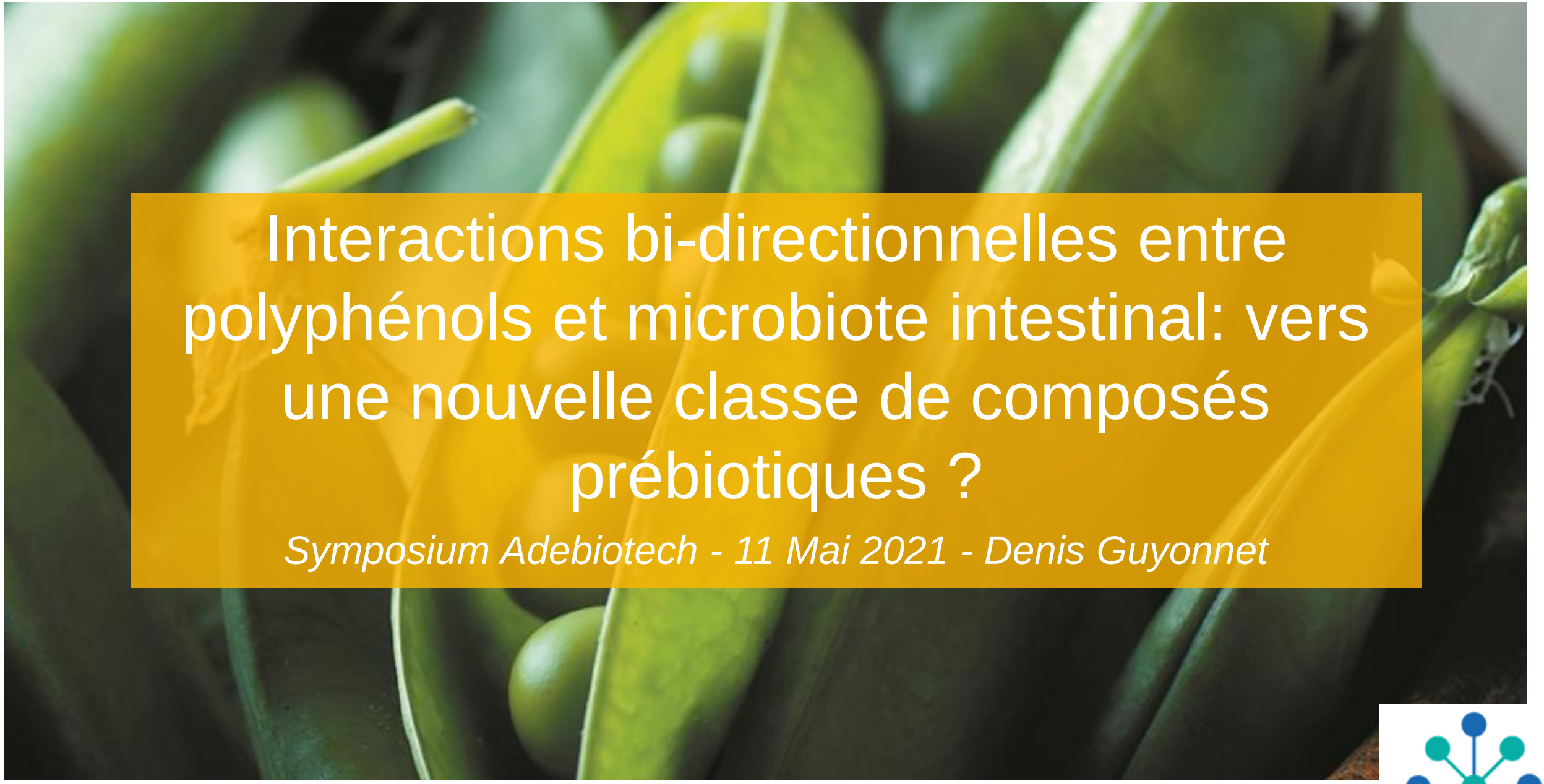


Interactions bi-directionnelles entre polyphénols et microbiote intestinal: vers une nouvelle classe de composés prébiotiques ?

Symposium Adebiotech - 11 Mai 2021 - Denis Guyonnet

diananova

ADEBIOTECH
THINK TANK ONE HEALTH

Nutrition Segment organization

A customer centric strategy with a customer driven organization

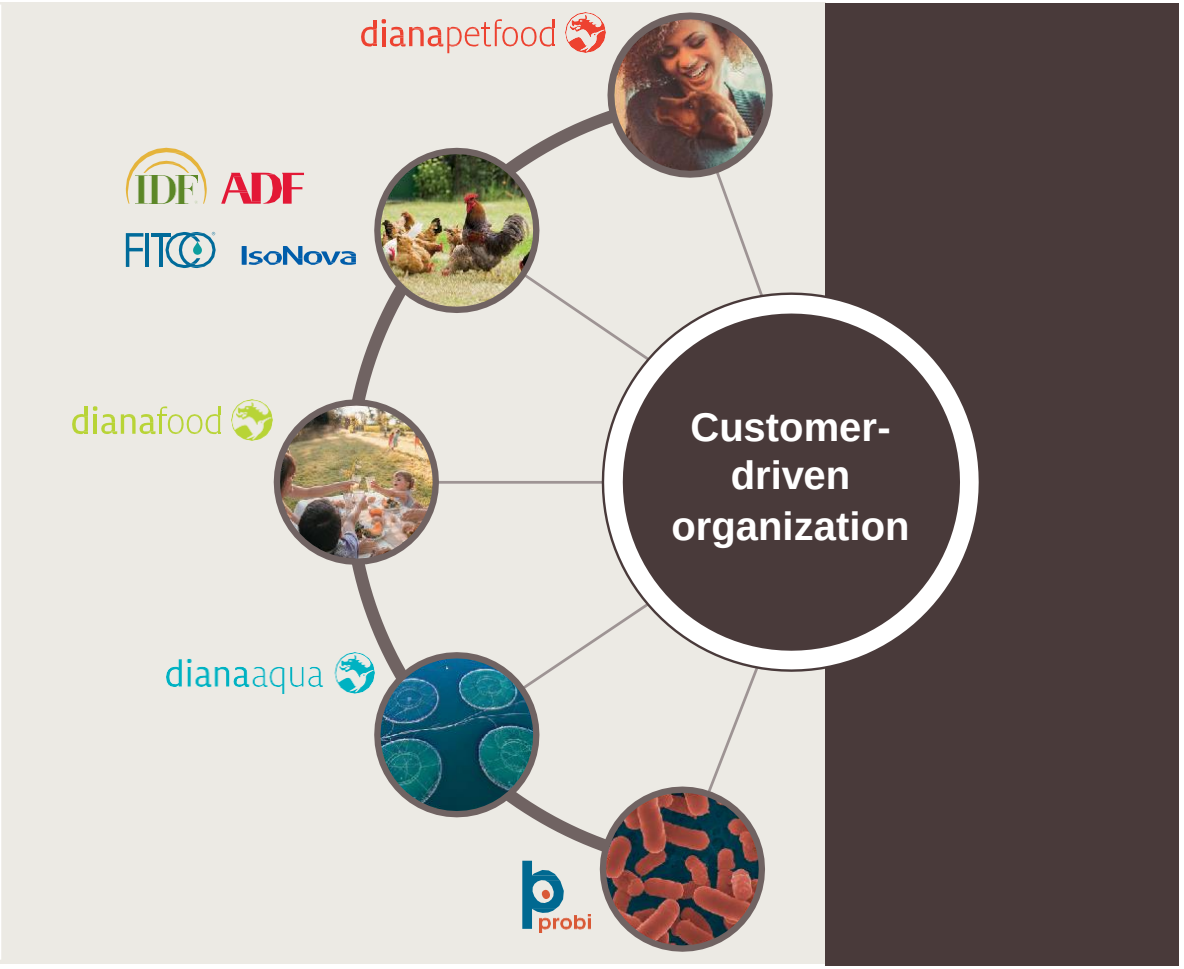
Diana Pet Food provides high-value solutions improving pet's well-being and owner's satisfaction.

ADF/IDF includes ADF, IDF, Isonova and FITCO companies. ADF/ IDF is a stream-driven leading US meat and egg-based protein specialist and pioneer in natural nutrition ingredients.

Diana Food offers consumer well-being solutions made from natural and sustainable ingredients for the food and beverage industry.

Diana Aqua develops and delivers advanced natural and sustainable solutions for the aquaculture feed industry.

Probi develops probiotics of the highest quality for food, beverage, and nutritional supplements industries with health-promoting benefits.



Nova is an incubator structure within Diana to accelerate development in Health & Nutrition

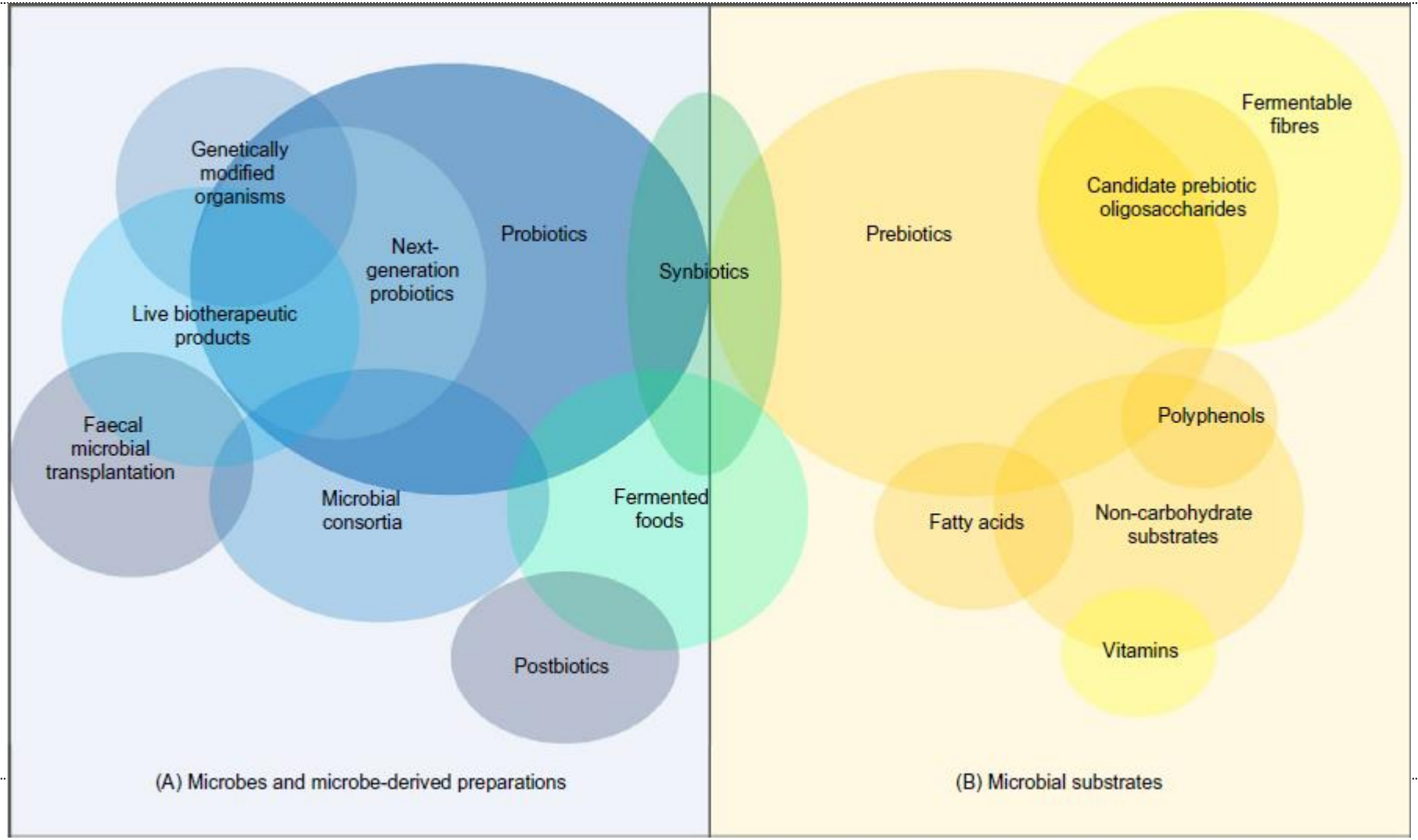
Its activities are currently focusing on 3 platforms:

Food Protection
A platform which develops natural antimicrobials and antioxidants in order to answer consumer's demands for cleaner and clearer solutions to food spoilage and food safety.

Side-Streams Valorization
A platform which explores how to improve the industrial valorization of fruit and vegetable side streams by developing research & innovation initiatives

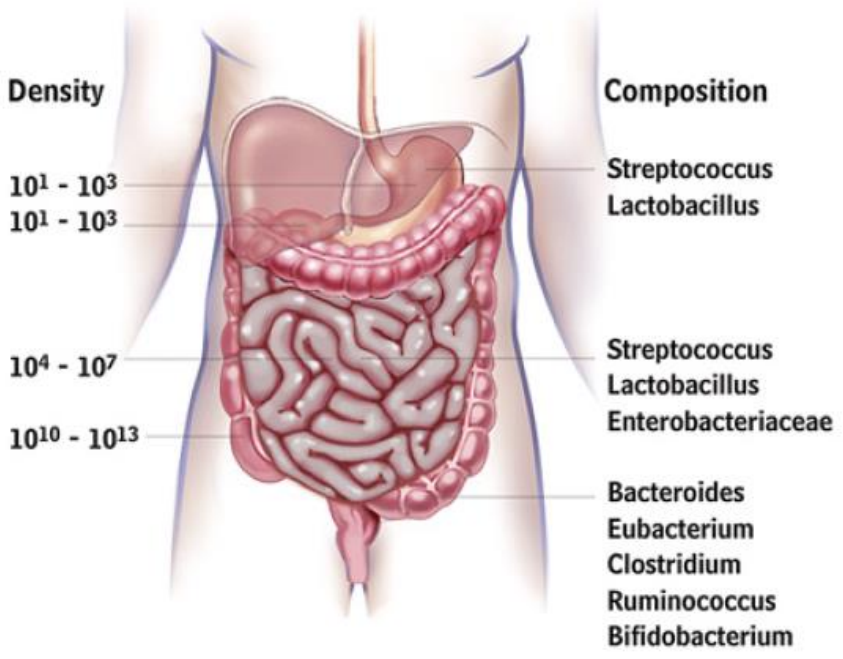
Gut Modulation
A platform which identifies the natural components of our raw materials (such as polyphenols, fiber and probiotics,) which have the highest impact on gut microbiota, and promote health through healthy nutrition.

Pro-, Pre- and synbiotics: a field of innovation in health & nutrition



From Cunningham *et al.*, *Trends in Microbiology*, 2021

Gut Microbiota: A Dynamic System



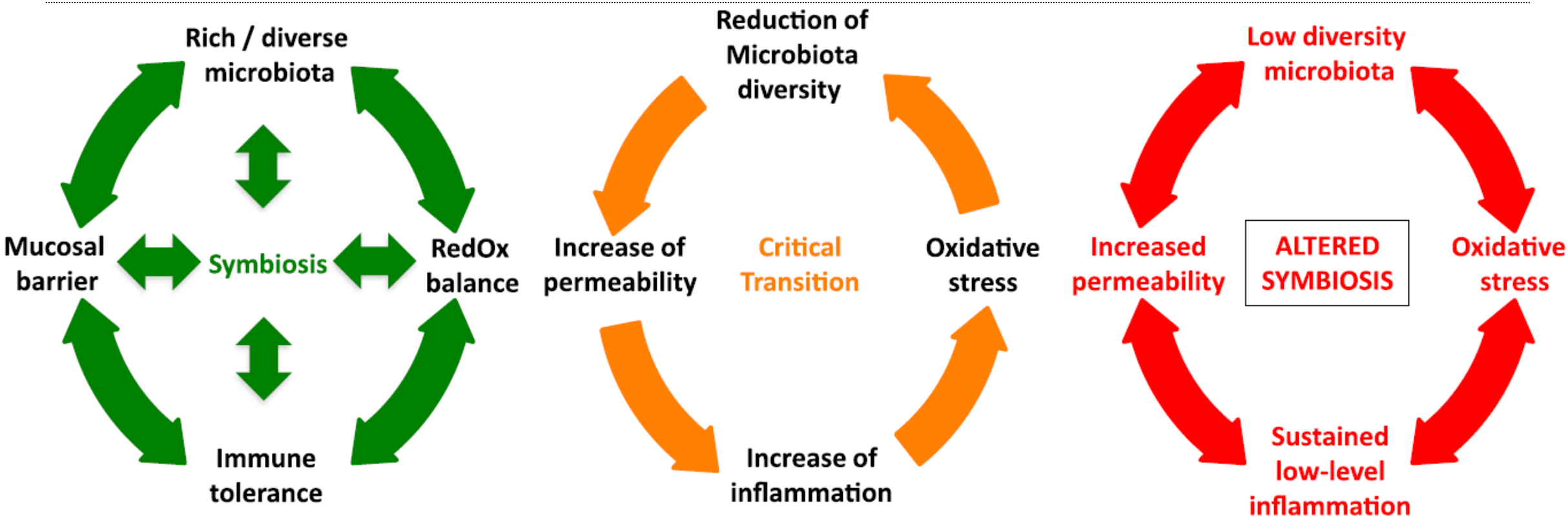
Intrinsic factors	Extrinsic factors
Gastric acid	Diet, Pre and probiotics
O_2	PPIs, H2 blockers
Motility	Antibiotics
Mucus	Prokinetics
GI secretions	Laxatives
Antimicrobial peptides	Opioids
Immunity (sIgA)	NSAIDs

Gut microbiota is also evolving through lifespan (e.g. decrease diversity in elderly) and its composition varies among individuals and depends on environmental factors (e.g. lifestyle, diet, drugs, stress),

Simrèn *et al*., *Gastroenterology*, 2012

Restoration of Gut Symbiosis with dietary strategy

Leveraging on multiple mechanisms of actions

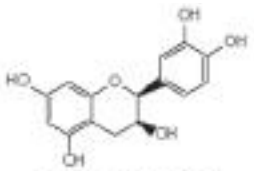


Adapted from van de Guchte *et al.*, *Microbiome*, 2018

Polyphenols: Family of phenolic compounds with high chemical diversity

High chemical diversity: > 8000 different structures

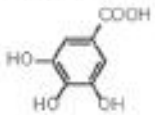
Flavonoids



epicatechin

- Flavonols — *quercetin*
- Flavanones — *hesperidin*
- Isoflavones — *daidzein*
- Anthocyanins — *cyanidin*
- Flavan-3-ols — *epicatechin gallate*
- *Proanthocyanidins (condensed tannins)*

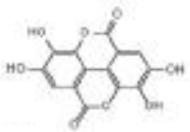
Phenolic acids



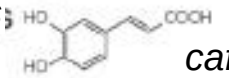
gallic acid

benzoic acids

hydroxycinnamic acids

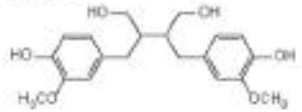


ellagic acid



caffeic acid

Lignans



secoisolariciresinol

Stilbenes

resveratrol

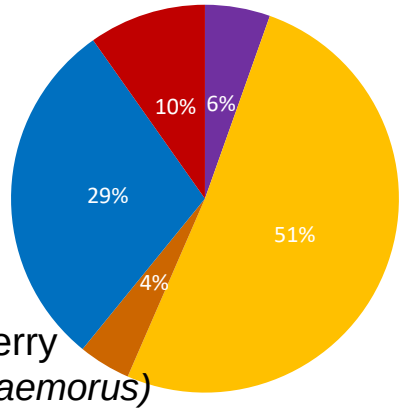
Dietary Consumption: 1200mg/day (Suvimax) – 585-1800 mg/day (EU & non-EU countries)

Perez-Jimenez *et al*., *AJCN*, 2011; Del Bo *et al*., *Nutrients*, 2019; Fraga *et al*., *Food Funct*, 2019

Not all polyphenols are the same

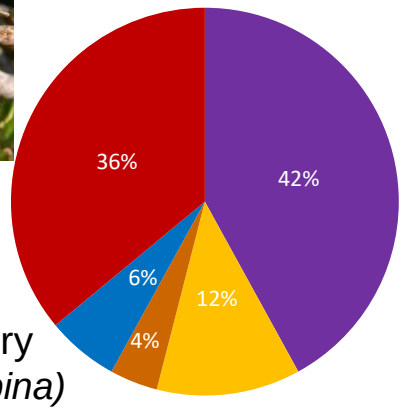
Polyphenol composition of 6 Nordic berries

72



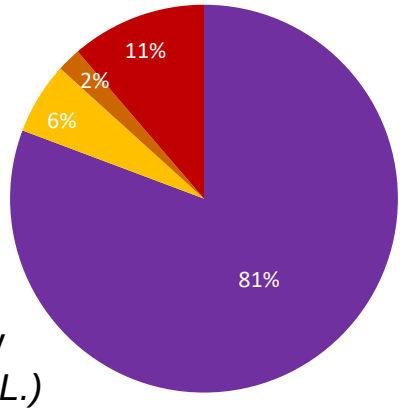
Cloudberry
(Rubus chamaemorus)

527



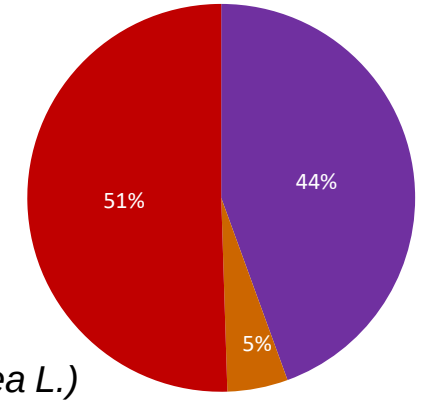
Alpine Bearberry
(Actostaphilos alpina)

454



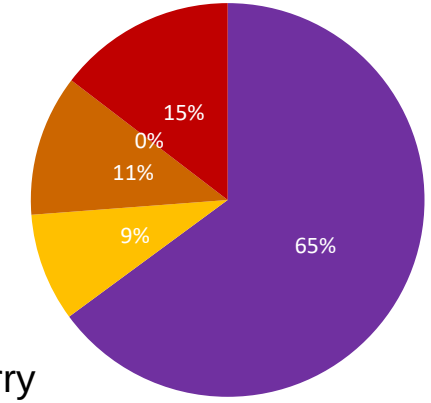
Black Crowberry
(Empetrum nigrum L.)

506



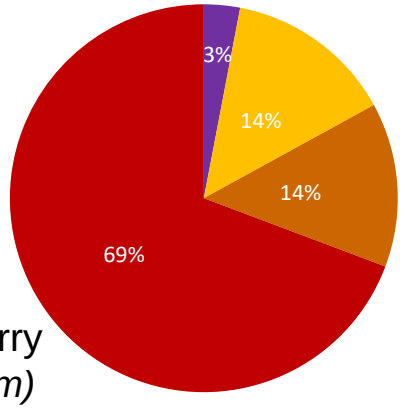
Lingonberry
(Vaccinium vitis-idaea L.)

603



Chokeberry
(Aronia melanocarpa)

762



Highbush cranberry
(Viburnum trilobum)

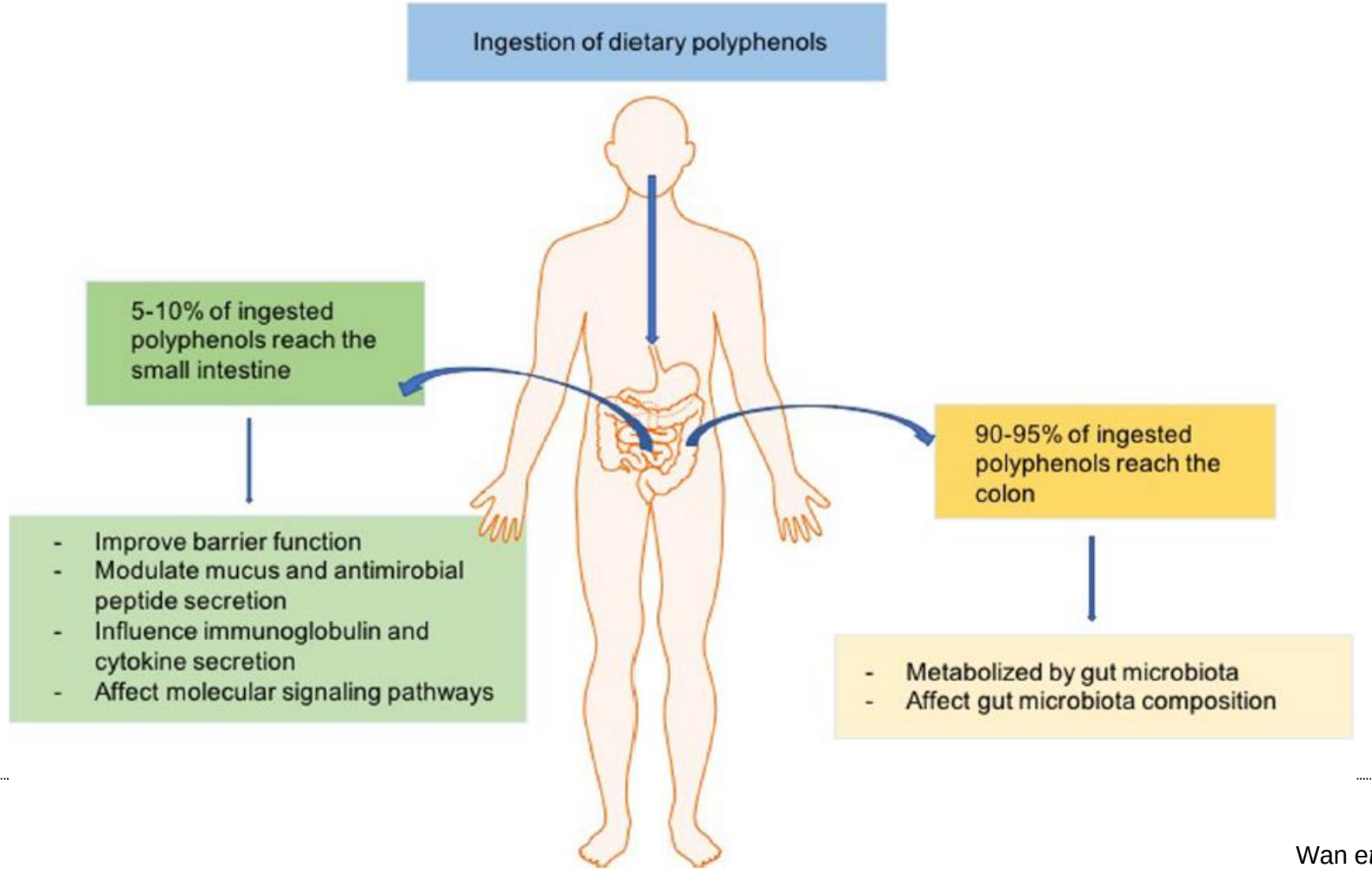
Ellagitannins Proanthocyanidins Anthocyanins

Phenolic Acids Flavonols/Flavanols

Total polyphenols (mg/100g fresh fruit)

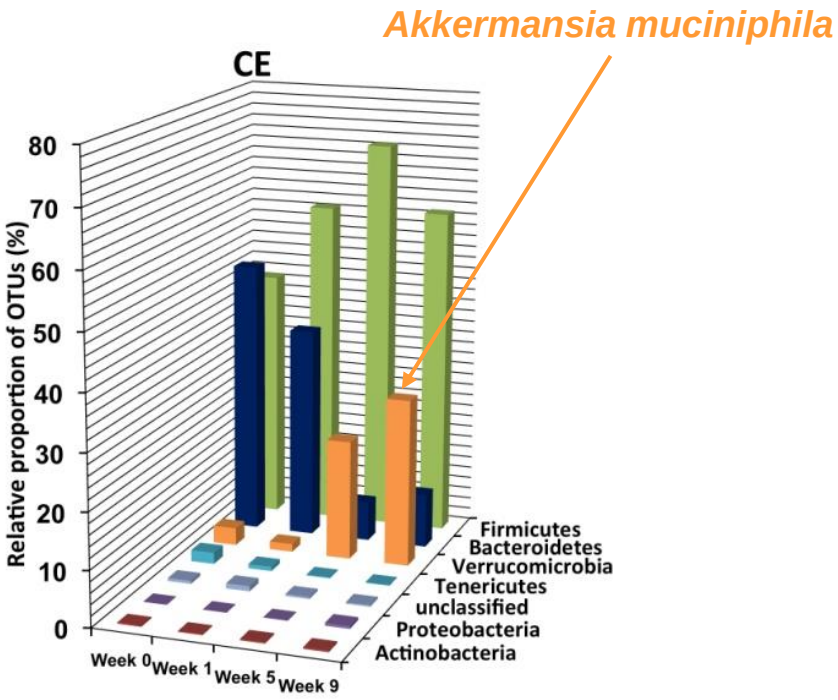
Dudonné *et al.*, *J Food Compo Anal*, 2015

Intestinal fate of polyphenol and impact on gut health

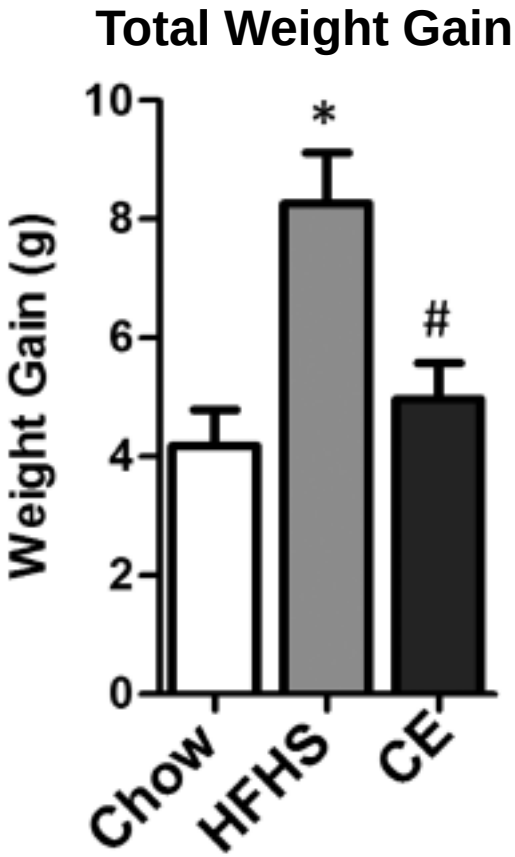


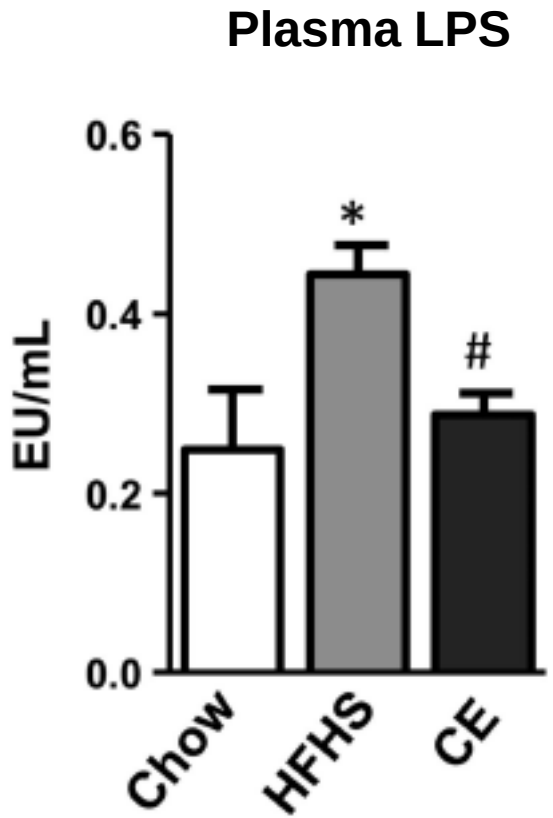
Wan et *al*., *Crit Rev Food Sci Nut*, 2020

Effect of polyphenol on gut microbiota : increase in *Akkermansia muciniphila* with proanthocyanidins



Cranberry Group
(200mg/kg daily)





Design: 8-week study, 12 mice/group

Similar effects have been observed with other fruit extracts rich in tannins (pomegranate, apple, blueberry, grape)

Anhê *et al*., *Gut*, 2014

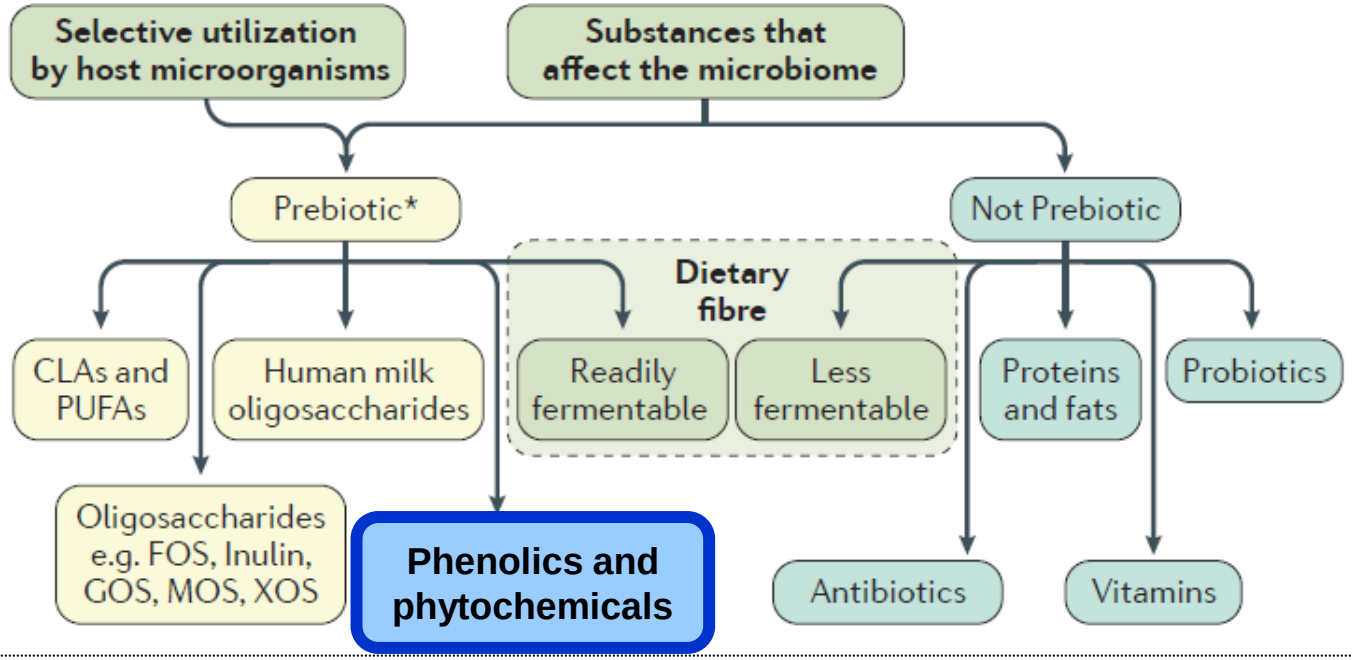
Effect of polyphenols on gut microbiota

- **Modulation of gut microbiota composition observed with different polyphenols**
- **Most of data obtained in rodent models**
- **No common effect shared by polyphenols**
- **Data in humans obtained in small sample size studies (15-50 subjects)**
- **Need for larger and well designed human studies with appropriate gut microbiota methods (eg metagenomics)**

Polyphenols can be considered as prebiotic

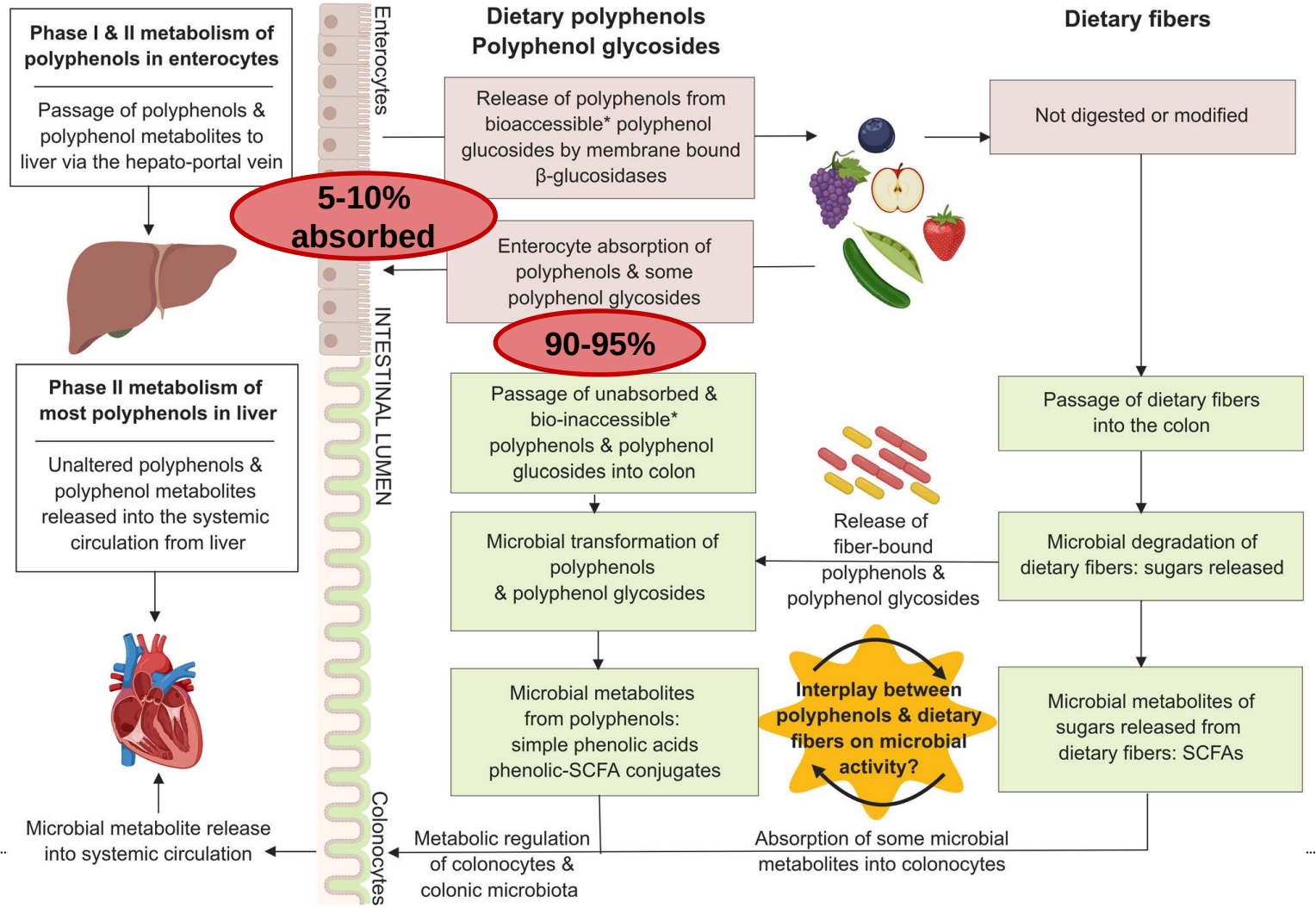
Prebiotics: a substrate that is selectively utilized by host microorganisms conferring a health benefit (ISAPP consensus definition, Gibson et al, 2017)

=> This new definition expands the concept of prebiotics to possibly include non-carbohydrate substances



Gibson *et al.*, *Nature Rev Gastroenterol*, 2017

Integrated view of intestinal metabolism of polyphenols and absorption



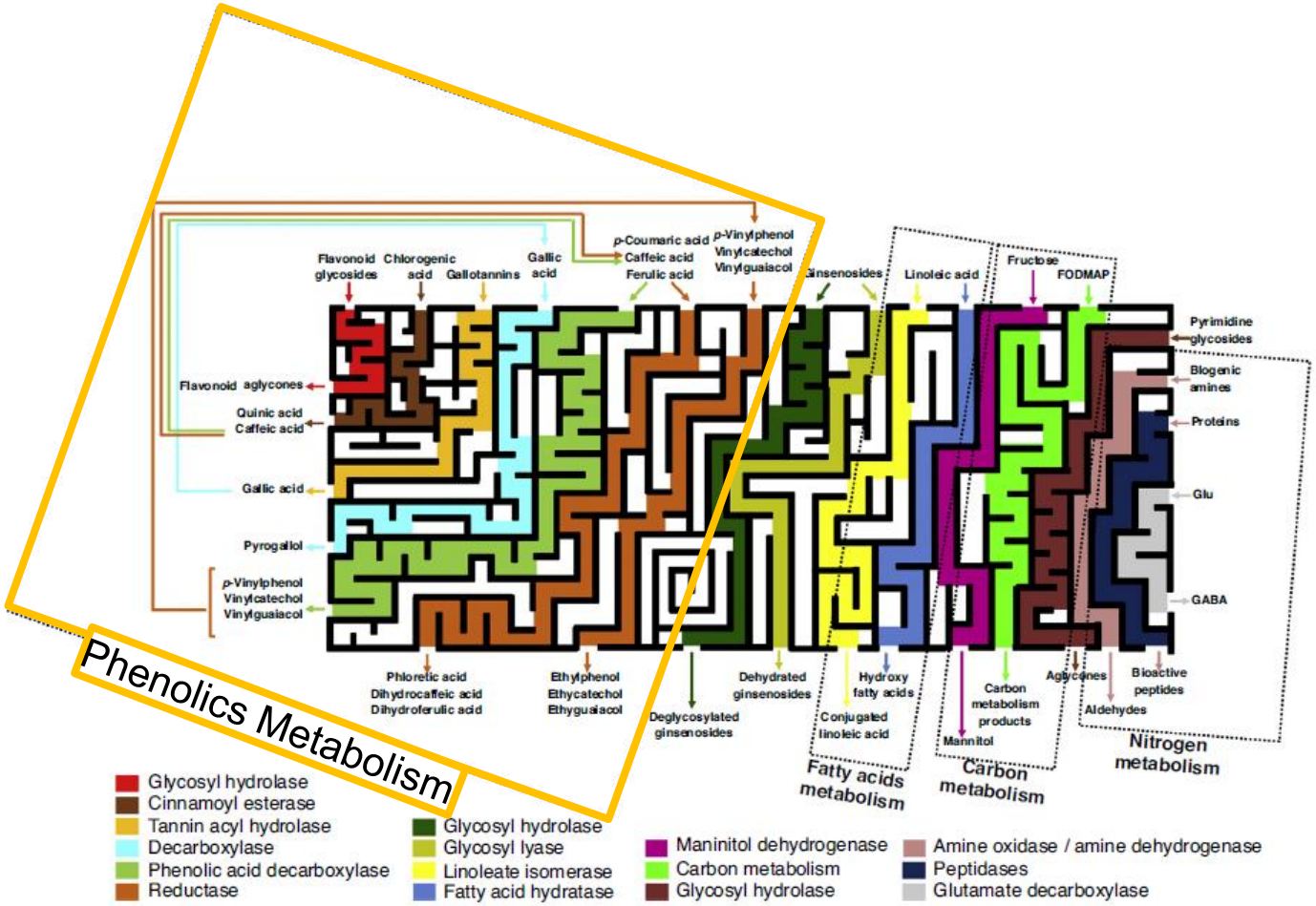
Loo *et al.*, *Compr Rev Food Sci Food Saf*, 2020

Enzymatic reactions catalysed by human gut microbiota

Enzymatic reaction	Polyphenols	Gut bacteria genus
O-glycosidase	Flavonols, anthocyanins	*Clostridium, Eubacterium, Enterococcus, Lactobacillus, Bifidobacterium*
C-glycosidase	Flavones, isoflavones	*Eubacterium, Enterococcus, Lactococcus*
Esterase	Hydroxycinnamic acid	*Lactobacillus, Bifidobacterium*
C-ring cleavage	Flavonols, flavanones, flavan-3-ols, anthocyanins	*Eubacterium, Flavonifractor, Eggerthella, Lactobacillus, Butyrivibrio, Slackia*
Lactone cleavage	Ellagitannins	*Gordonibacter, Ellagibacter*
Dehydroxylation	Flavanones, flavonols, tannins, flavan-3-ols, anthocyanins	*Clostridium, Eubacterium, Flavonifractor, Eggerthella, Gordonibacter, Ellagibacter*
Demethylation	Flavanones, flavonols, flavan-3-ols, anthocyanins, lignans	*Eubacterium, Blautia, Lactobacillus, Streptococcus*
Decarboxylation	Tannins, benzoic acid, Hydroxycinnamic acid	*Gordonibacter, Ellagibacter*
Reduction	Isoflavones, lignans, stilbenes	*Bifidobacterium, Eggerthella, Slackia, Adlercreutzia*

For details & review: Cortés-Martin *et al*., *Mol Nutr Food Res*, 2020

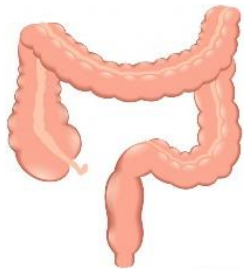
Metabolism of phenolic compounds by lactic acid bacteria (*Lactobacillus*, *Bifidobacteria*)



From Filannino *et al*, *Curr Opin Biotechnol*, 2018

Metabotype concept: Clustering according to the ability to produce different metabolites of ellagitannins

Colonic Gut Microbiota Metabolism



Dietary Ellagitannins (e.g. pomegranate, walnut)

Ellagic acid

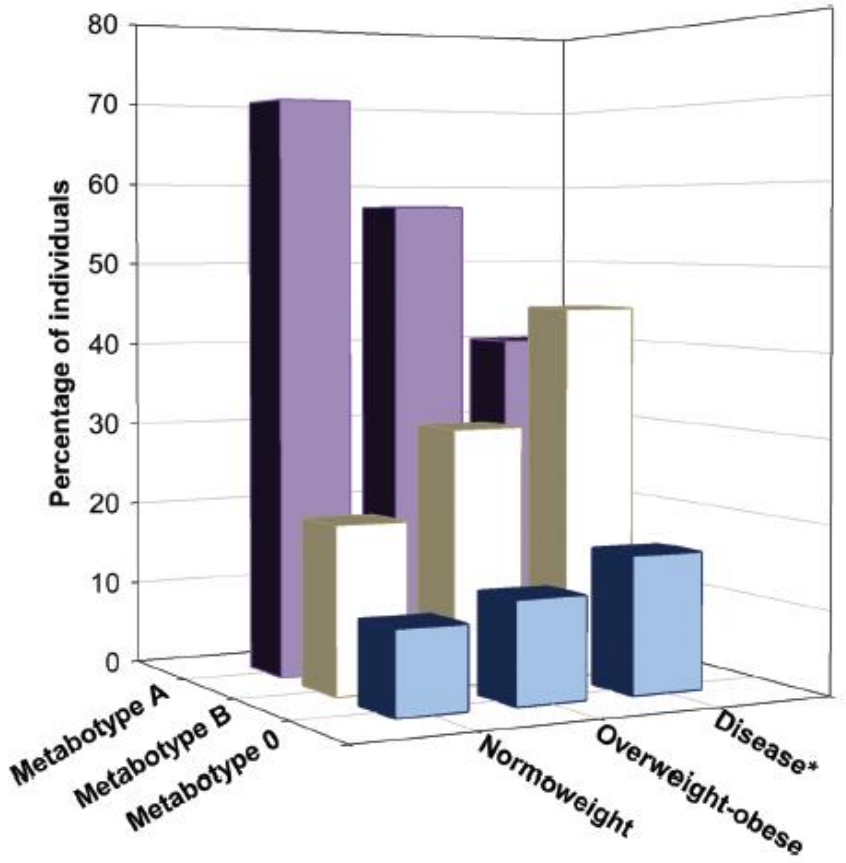
Urolithin A	Urolithin A + Isourolithin A and/or Urolithin B	No Urolithin
Metabotype A	**Metabotype B**	**Metabotype 0**

Positive correlation between *Gordonibacter* & urolithin A
Higher *Gordonibacter* level in metabotype A vs. metabotype B
Negative correlation between *Gordonibacter* & metabotype B

***Ellagibacter isourolithinifaciens produces iso*urolithin A**
Positive correlation between *Ellagibacter* &metabotype B

García-Villalba *et al., J Agric Food Chem, 2017;* Selma *et al.*, *Food Function*, 2017; Romo-Vaquero *et al.*, *Mol Nutr Food Res*, 2019

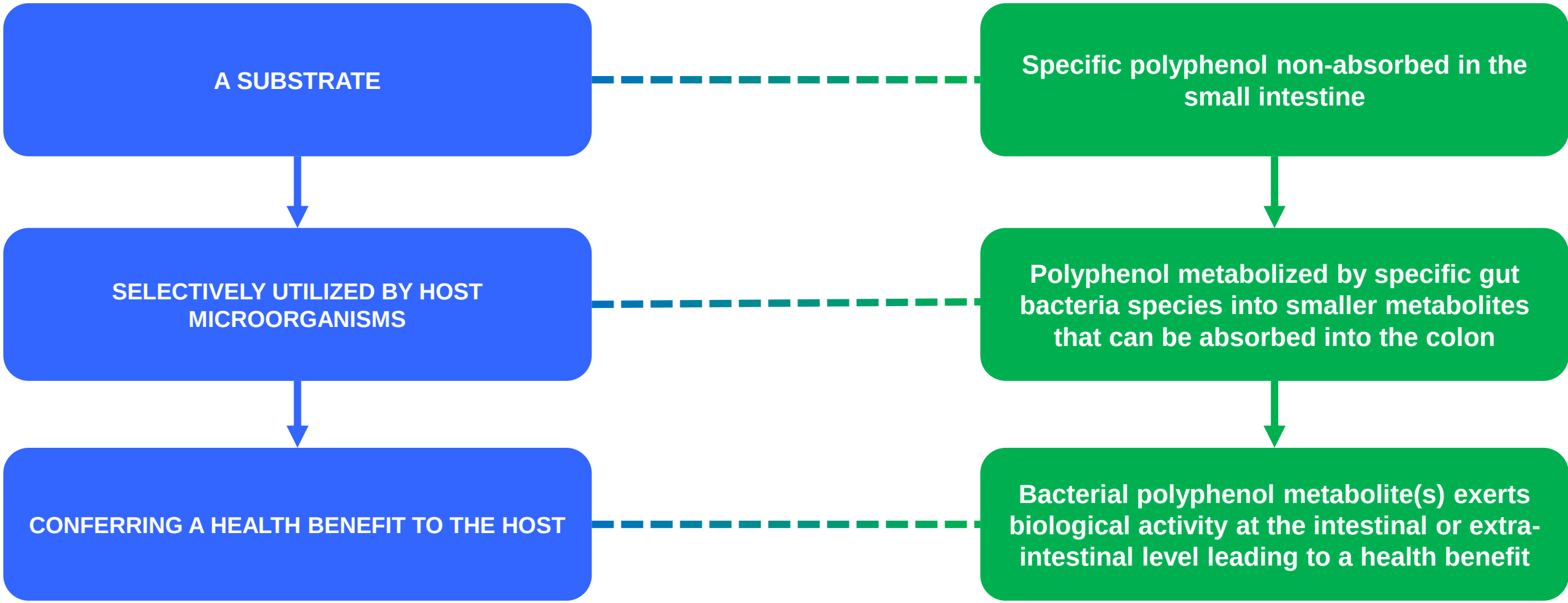
Prevalence of urolithin metabotype in healthy subjects, overweight-obese and disease patients



Mean distribution percentage of the three urolithin-producing metabolic metabotypes present in healthy normoweight (n = 20), overweight/obese subjects (n = 49) and patients with disease (metabolic syndrome (n = 41) and colorectal cancer (n = 26)).

Tomás-Barberán *et al*, *J Agric Food Chem*, 2014; Selma *et al*., *Food Function*, 2017

How to translate prebiotic definition* for polyphenols?



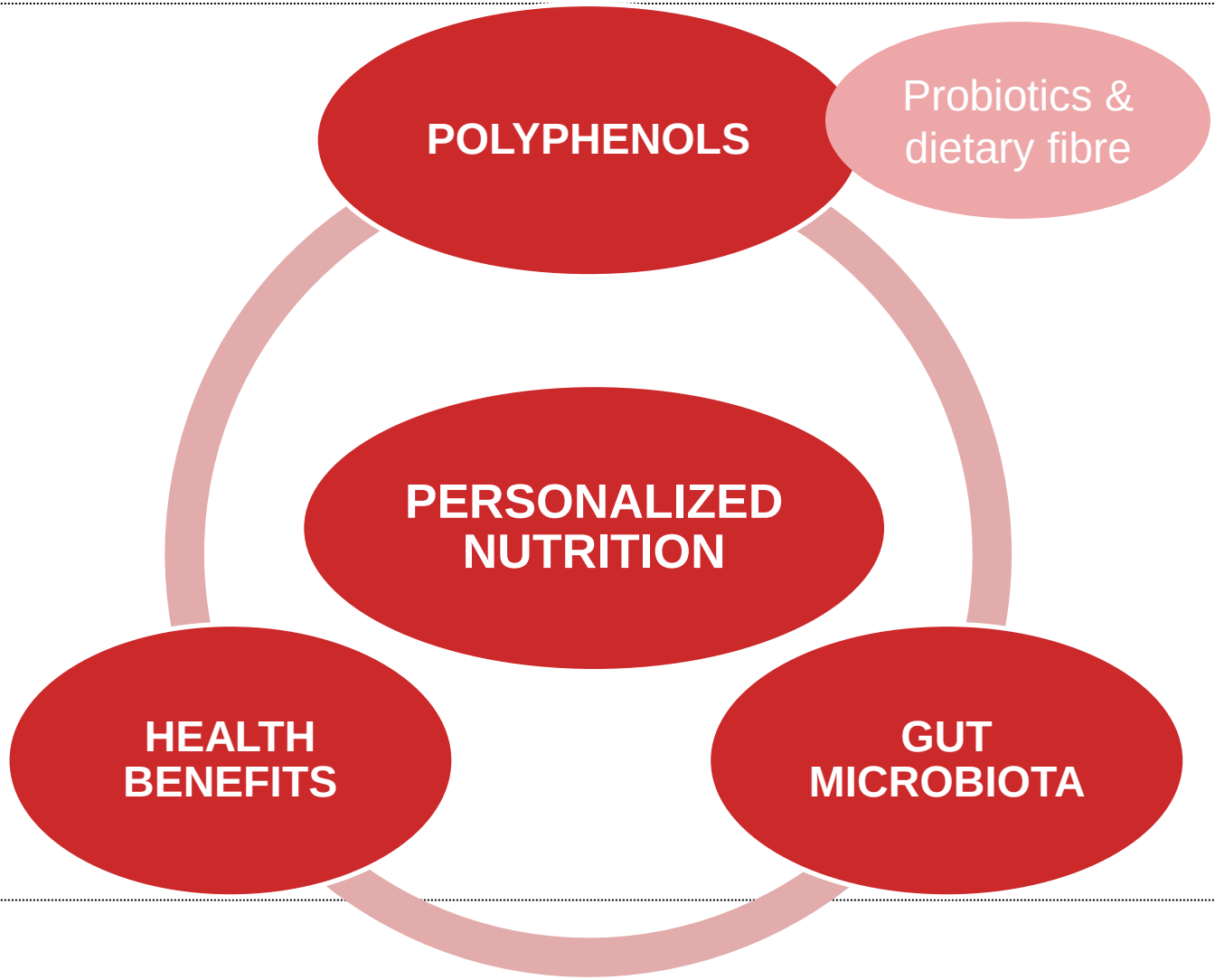
*_Prebiotics_: ISAPP consensus definition (Gibson *et al.*, *Nat Rev Gastroenterol*, 2017)

Challenges & Opportunities

- **Characterize the metabolic pathways for the different types of polyphenols**
- **Identify people harbouring the required gut microbiota species to metabolize polyphenols**
- **Demonstrate the link between metabolism of polyphenols & health benefit**

- **Develop a new category of natural prebiotics**
- **Implement personalized dietary strategy**
- **Potential 2nd generation probiotics based on their ability to metabolize polyphenols**

Integrated view of the development of new natural dietary products with polyphenols



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denis.guyonnet@symrise.com