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Exploring the role of the major gut microbiota clusters on nutritional and functional benefits of nutrients and non-nutrients

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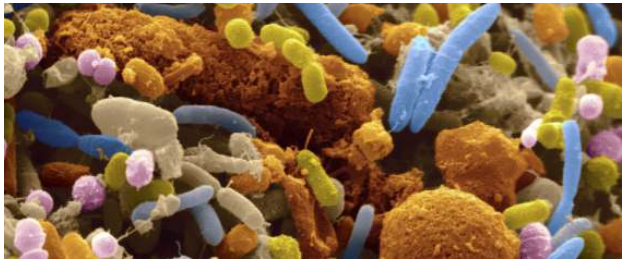

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Conflict of Interest Disclosure

This work was conducted by an expert group of the European branch of the International Life Sciences Institute, ILSI Europe. The non-industry members within this expert group were offered support for travel and accommodation costs to attend meetings for discussing the manuscript, and a small compensatory sum (honorarium) with the option to decline.

ILSI Europe group: 'Role of microbiota on nutritional & functional benefits of nutrients & non-nutrients'

Aims of the expert group

- Evaluate role of microbiota in metabolism of dietary compounds
- Review mechanisms and pathways involved
- Identify main types of microorganisms involved
- Consider the methodologies for investigating gut microbiota metabolism

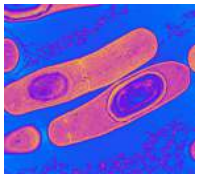
Outputs

Shortt *et al* 'Systematic review of the effects of the intestinal microbiota on selected nutrients and non-nutrients' Eur J Nutr. 2017

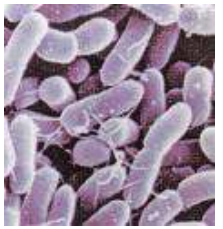
Rowland *et al* 'Gut microbiota functions: metabolism of nutrients and other food components' Eur J Nutr. 2017 Apr 9.

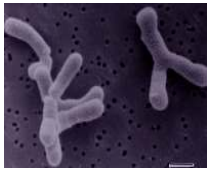
Human gut microbiota – phyla & genera

- Firmicutes
  - *Clostridium*
  - *Roseburia*
  - *Faecalibacterium*
  - *Blautia*
  - *Dorea*
  - *Lactobacillus*
  - *Peptostreptococcus*
  - *Eubacterium*
  - *Streptococcus*
  - *Staphylococcus*
  - *Butyrivibrio*



- Bacteroidetes
  - *Bacteroides*
  - *Prevotella*
- Verrucomicrobia
  - *Akkermansia*
- Proteobacteria
  - *Escherichia*
  - *Klebsiella*
  - *Desulfovibrio*
- Actinobacteria
  - *Bifidobacterium*
  - *Collinsella*





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90% of bacteria are in Bacteroidetes/ Firmicutes phyla

Gut microbiota - metabolism

- Large metabolic potential - equivalent to, but different from that of **liver**

- Microbiota metabolic range
  - Reduction
  - Hydrolysis
  - Polysaccharide fermentation
  - Dehydroxylation
  - Methylation
  - Demethylation
  - Deamination
  - Nitrosation
  - Ring fission
  - Aromatization
  - Oligomer breakdown

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Dietary components reviewed

- Carbohydrates
- Energy homeostasis
- Proteins
- Lipids
- Bile acids
- Vitamins
- Phytochemicals/polyphenols

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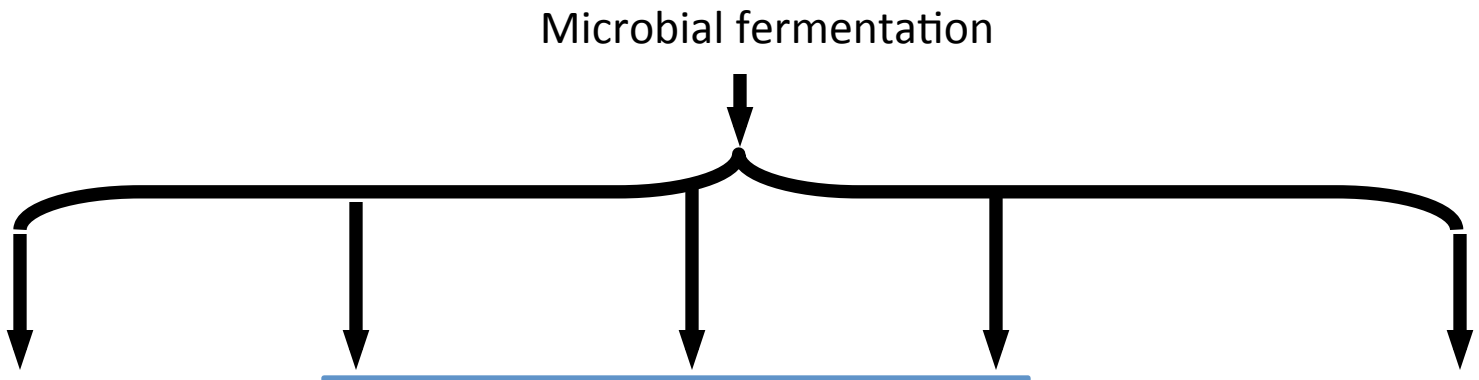
Carbohydrate fermentation

Polysaccharides
NSP/Resistant starch

Oligosaccharides

Mucins



H_2 CO_2

CH_4

Acetate

Propionate

Butyrate

Lactate

Methanobrevibacter smithii

Most gut organisms

Eubacterium hallii
Roseburia
Coprococcus catus
Megasphera elsdenii
Veillonella spp
Ruminococcus obeum
Bacteroidetes

Eubacterium rectale
Eubacterium hallii
Roseburia spp
Coprococcus spp
Faecalibacterium prausnitzii

Bifidobacterium spp
Lactobacillus spp

H_2S

Desulfovibrio spp

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Energy homeostasis

Studies in humans and animals suggest microbiota is involved in assimilation, storage & expenditure of energy obtained from dietary substrates.

- Some studies report higher Firmicutes/Bacteroides ratio in obese subjects
- Higher BMI associated with increased abundance of *Eubact. ventrosium* and *Roseburia intestinalis*, *E. rectale*
- Weight-loss regimes (diet or gastrectomy) associated with ⇑ Bacteroidetes ⇓ Firmicutes inc *Clostridium, Eubacterium, Coprococcus)*.

Potential mechanisms

- Gut microbes break down non-digestible carbohydrates to SCFA allowing the host to salvage energy from indigestible dietary substrates.
- SCFA ⇓ energy intake : Pr & Bu increase the levels of satiety hormones PYY and GLP-1, Ac & Pr increase expression of leptin

  Role of specific gut microbes and SCFA in energy balance remains to be clarified

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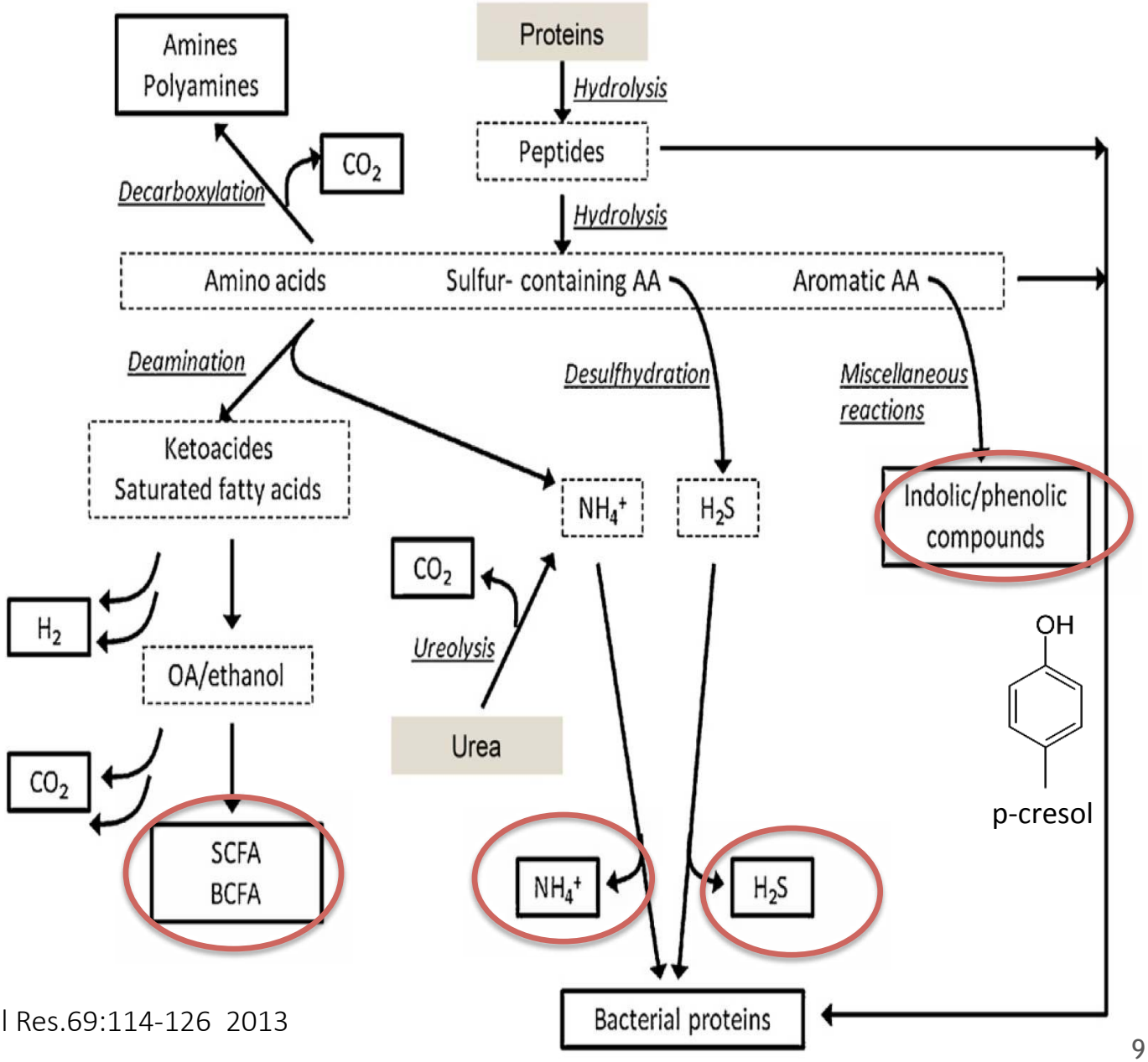
Protein metabolism

clostridia
peptostreptococci
peptococci

Bacteroides spp
Eubacterium hallii
Clos barlettii



Branched chain fatty acids (BCFA)
- Isobutyrate (from val)
- 2-methylbutyrate (i-leu)
- Isovalerate (leu)

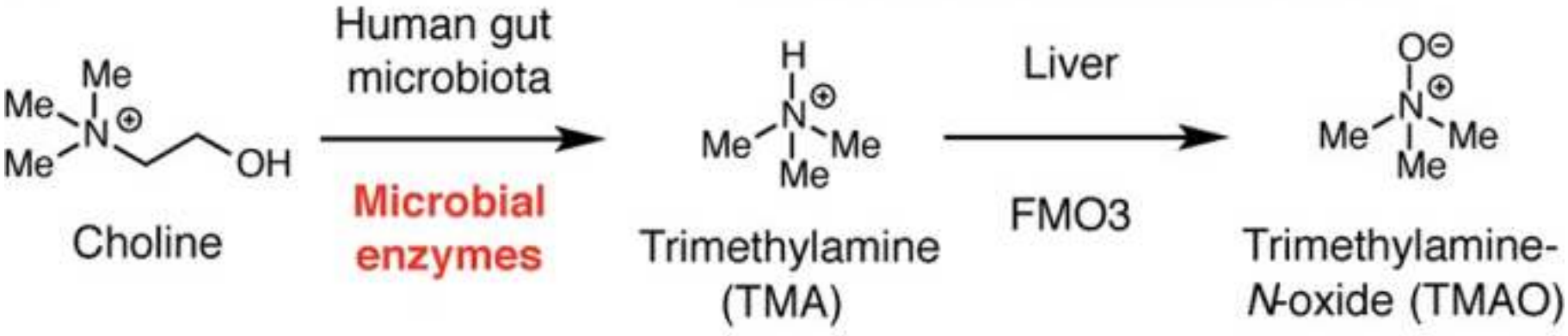
Davila *et al.* Pharmacological Res.69:114-126 2013

Lipid metabolism

- Linoleic acid reduced to stearic acid (via CLA and vaccinic acid) in vitro by range of gut bacteria

- Phosphatidylcholine to TMA

Microbiota metabolism of choline to TMA and TMAO



TMA produced by solely by gut microbiota
High-fat diets lead to increased production of TMA and TMAO, - risk factors for cardiovascular disease

Choline metabolizers:
Proteobacteria *: Desulfovibrio desulfuricans, Klebsiella spp, Escherichia spp, Edwardsiella tarda, Proteus penneri*
Firmicutes: *Clos sporogenes, hathewayi, asparagiforme*

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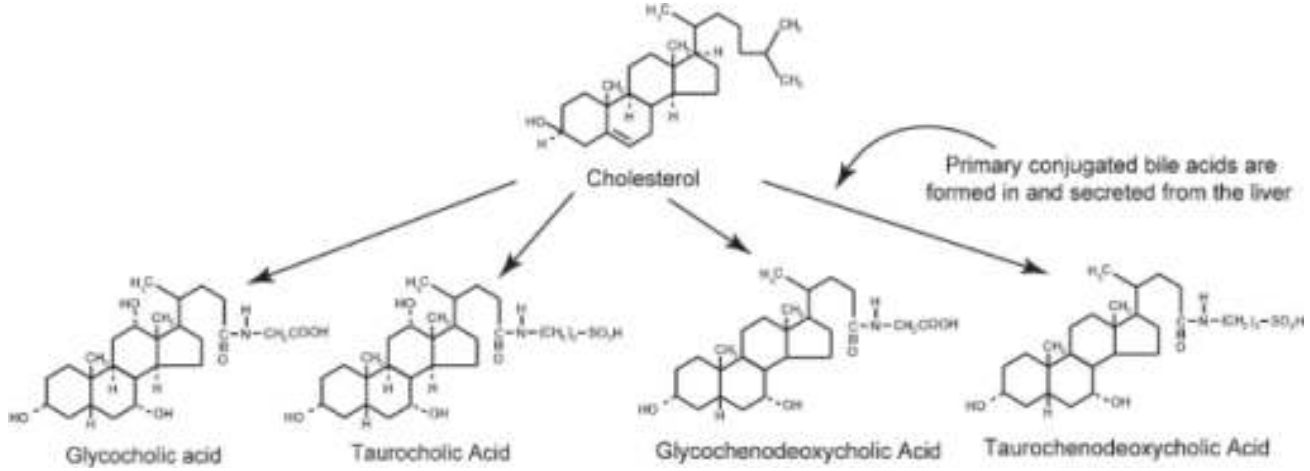
Martinez-del-Campo mBIo 6(2) e00042 (2015)
Romano et al mBio 6(2) e02481 (2015)

Bile acids

1. Deconjugation by bacterial **bile salt hydrolases (BSH)**



←Bile salts

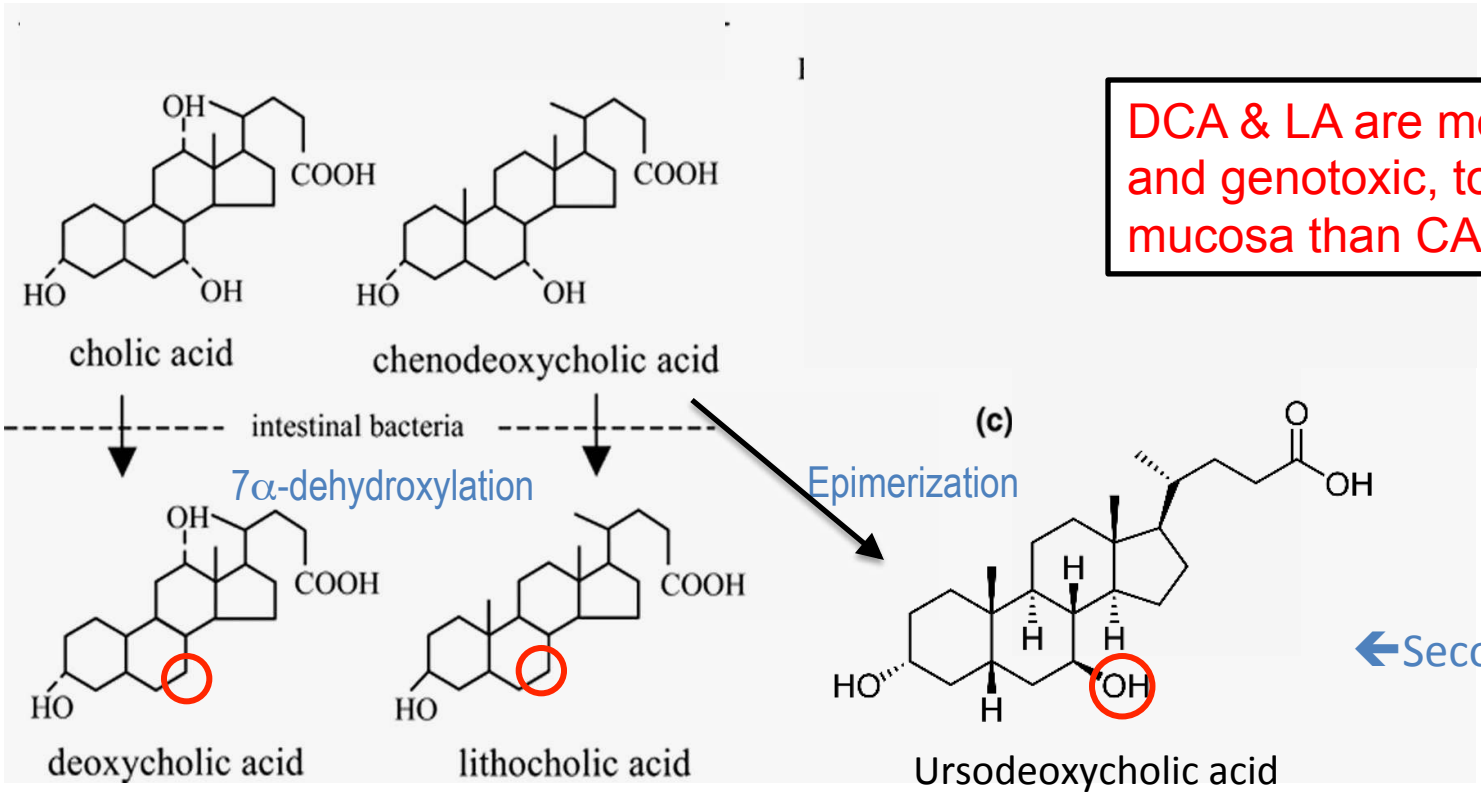
↓ BSH

←Bile acids

Bile salt hydrolase

- BSH genes identified in the main bacterial genera including *Bacteroides, Bifidobacterium, Clostridium, Lactobacillus,* and *Listeria*
- Most hydrolyze both glyco and tauro-conjugates.
- Reduces toxicity of bile acids, releases N, S and C atoms
- Deconjugation reduces efficiency of BA for emulsifying lipids and micelle formation

Bile acids – further metabolism



DCA & LA are more cytotoxic and genotoxic, to colon mucosa than CA & CDA

←Secondary bile acids

7-α-dehydroxylase

- main bacterial genera include *Clostridium, Eubacterium*

Epimerization

- Main genera : *Bacteroides, Clostridium, Egghertella, Peptostreptococcus, Ruminococcus, Eubacterium*

Vitamin synthesis

- Vitamin synthesis genes common esp. vitamin K and B group vitamins - biotin, cobalamin, folate, nicotinic acid, panthothenic acid, pyridoxine, riboflavin and thiamine
- For riboflavin & biotin, all tested microbes in Bacteroidetes Fusobacteria and Proteobacteria phyla had required pathways, fewer Firmicutes and Actinobacteria had the pathways
- Bacteroidetes is most important phyla for vitamin synthesis
- Many of these vitamins are utilized by other bacteria

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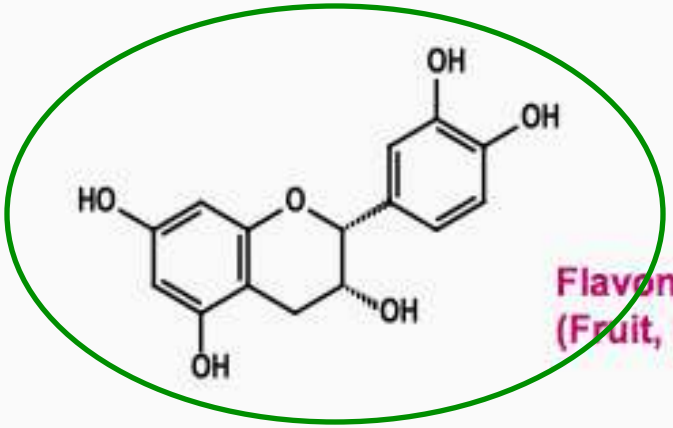
Vitamin synthesis

Vitamin	Intracellular concentration [mmol/gDW]	Dietary reference intake [mg/ day]	%DRI from gut microbiota
Biotin	9.0×10^{-7}	0.03	4.5
Cobalamin	8.5×10^{-8}	0.0024	31
Folate	5.0×10^{-5}	0.4	37
Niacin	3.3×10^{-3}	15	27
Pantothenate	2.3×10^{-6}	5	0.078
Pyridoxine	5.8×10^{-4}	1.3	86
Riboflavin	9.0×10^{-6}	1.2	2.8
Thiamin	8.7×10^{-6}	1.15	2.3

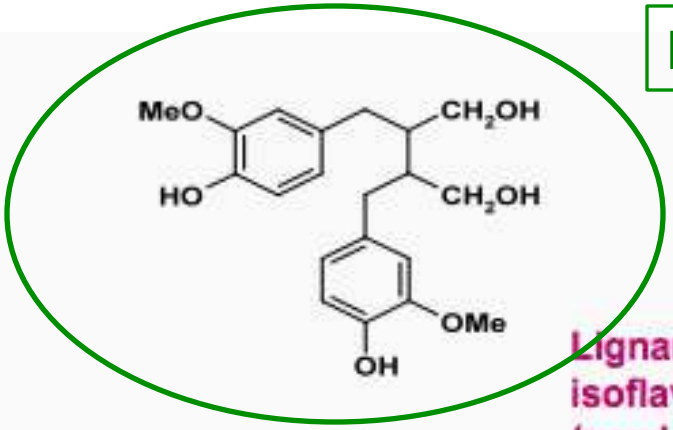
Magnusdottir *et al*. Front Genet. 2015

Phytochemicals

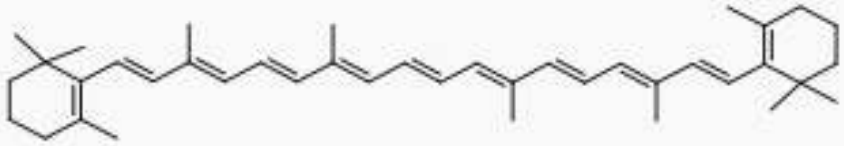
Polyphenols



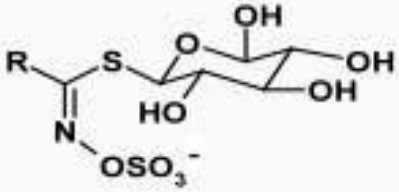
Flavonoids
(Fruit, veg.)



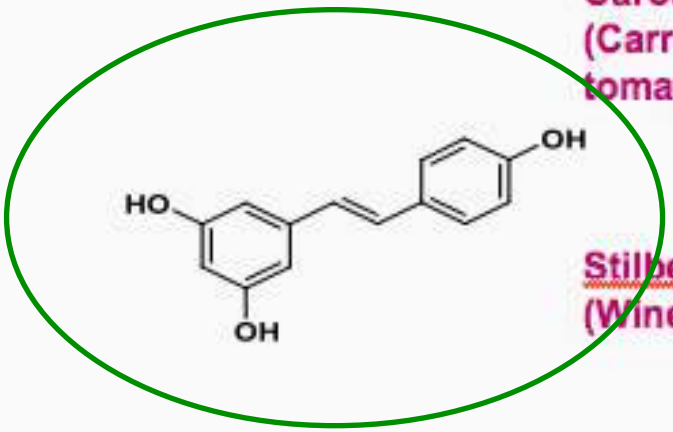
Lignans, ferulic acid, isoflavones
(seeds, cereals. legumes)



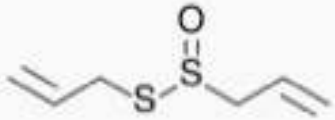
Carotenoids
(Carrot, pepper, tomato)



Glucosinolates/ Isothiocyanates
(cruciferous vegetables)



Stilbenes
(Wine, nuts)



Organosulphur Compounds
(Garlic, onions)

Polyphenols

- Often poorly absorbed in small intestine ➔colon
- Parent polyphenols are extensively metabolized by the microbiota, (deglycosylation, ring fission, dehydroxylation) - can impact bioactivity
- Metabolism often requires consortia or 2 or more microbes
- Large interindividual variations in absorption and excretion ascribed to differences in gut microbiota

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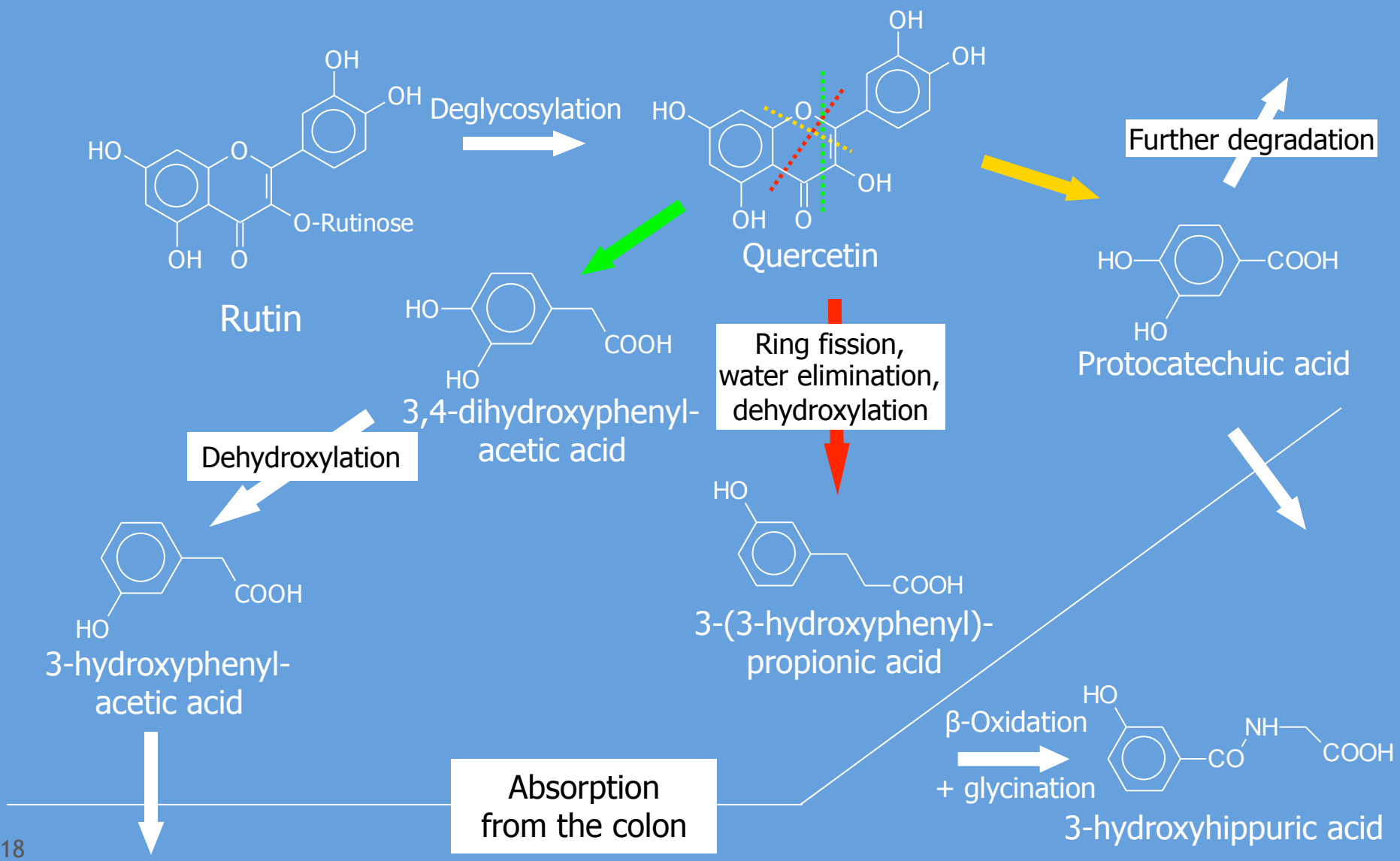
Pathways of colonic degradation of the flavonoid rutin



Gut microbiota & inter-individual variation in polyphenol metabolism

- Differences in composition of microbiota between individuals can have significant effects on extent of metabolism and metabolite profile
- Examples:
  - Isoflavonoids (daidzein to equol)
  - Naringin
  - Anthocyanins
  - Lignans
  - Tea catechins
  - Rutin

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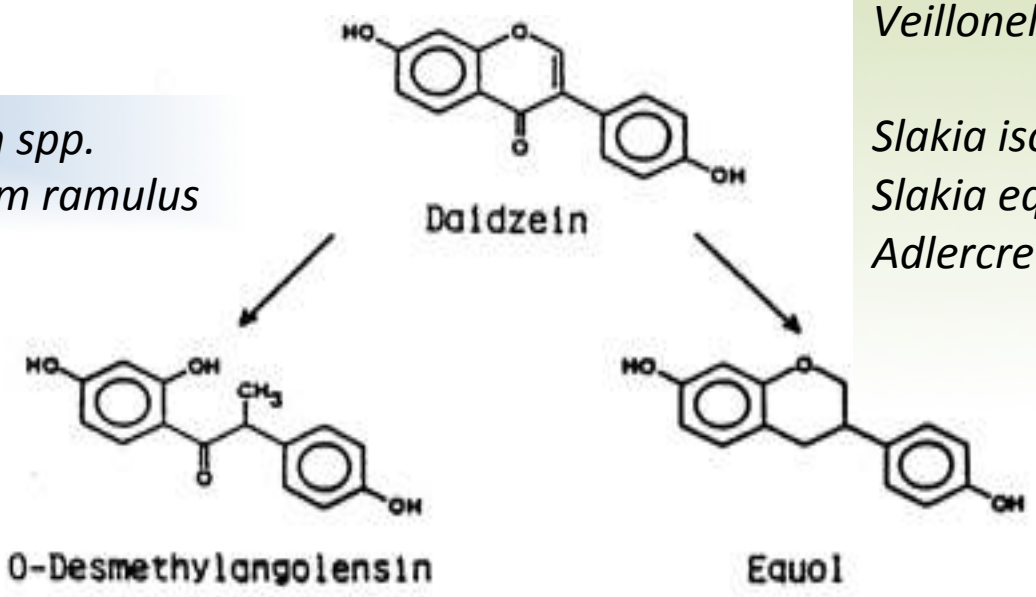
Isoflavone metabolism by gut bacteria

Clostridium spp.
Eubacterium ramulus



Lactobacillus mucosae +
Enterococcus faecium +
Finegoldia magna +
Veillonella sp

Slakia isoflavoniconvertens,
Slakia equolifaciens,
Adlercreutzia equolifaciens

Blaut et al 2003; Decroos et al 2005;
Matthies et al 2009, 2012)

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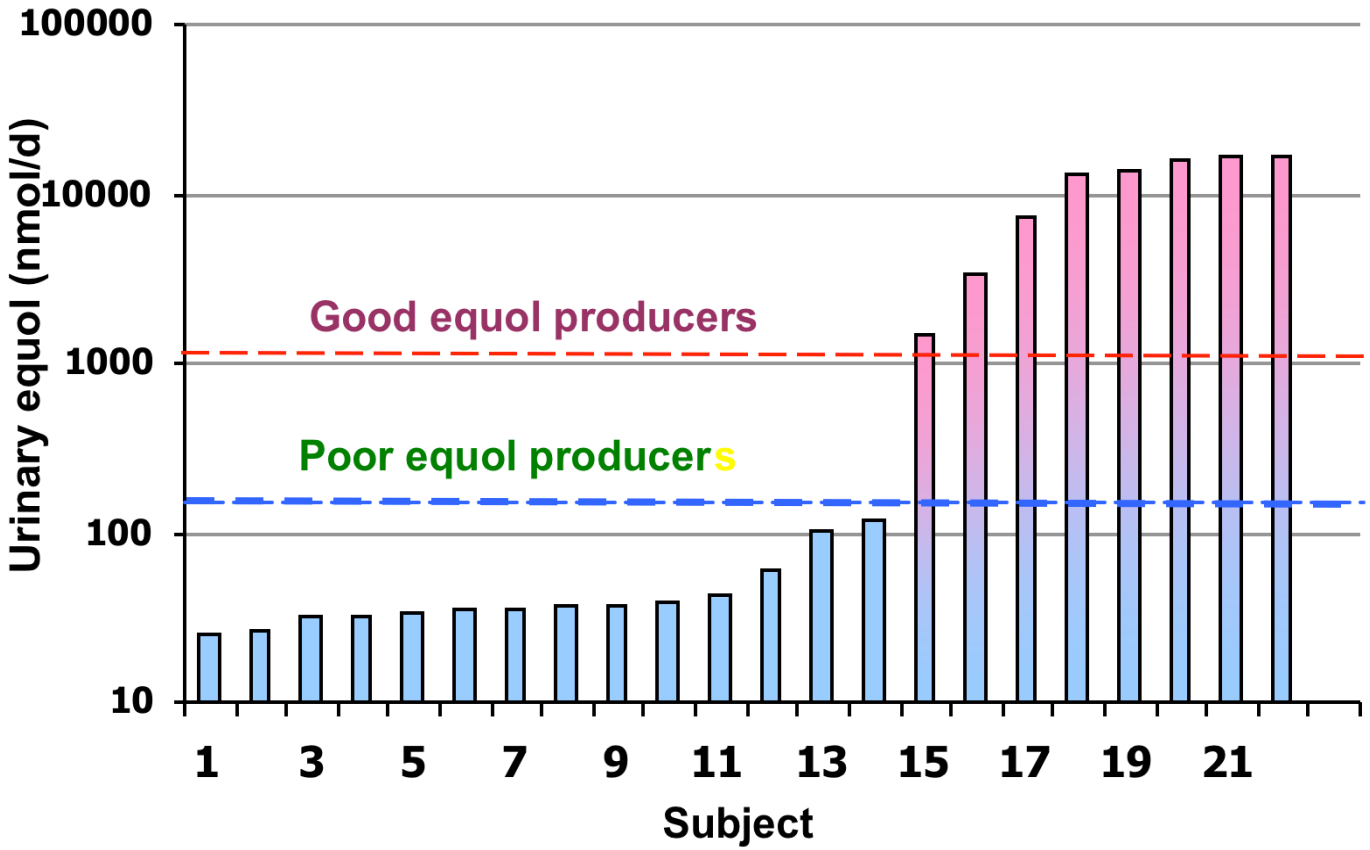
Equol excretion in subjects consuming soy isoflavonoids



Subjects consumed soy burgers (56mg IF) - 1/day for 17days (Rowland et al 2003)

Methodologies

- Isolated cultures
- Gut microbial enzyme activity
- Omics approaches
  - Metagenomics
  - Metatranscriptomics
  - Metaproteomics
  - Metabolomics
- Mathematical modeling

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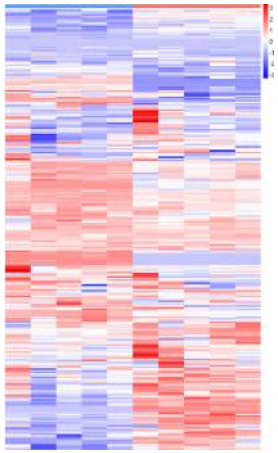
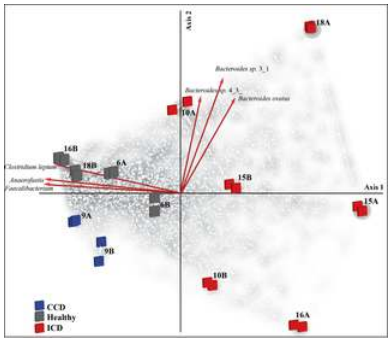
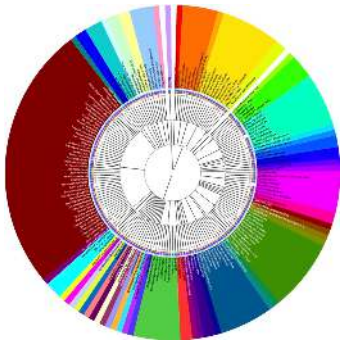
Omics approaches for studying gut microbial metabolism/function



- Metagenomics – study functional genes associated with specific microbial types,
- Meta-transcriptomics – monitor active bacteria, reveals functional roles (eg CHO metabolism) info on functional dysbiosis,
- Meta-proteomics – confirming microbial function (faecal meta proteome is subject-specific and stable)
- Metabonomics – pathway analysis, metabolic biomarkers of disease risk





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Conclusions

- Gut microbiota metabolism enlarges the capacity of host to metabolize range of dietary components and extends the range of metabolites formed
- CHO metabolism is major function of microbiota – pathways and microbes well studied.
- Microbial metabolites of nutrients and non-nutrients can be important cell signaling molecules (SCFA, bile acids) and have impacts on health (SCFA, TMA, phenolics)
- Large interindividual variation in microbiota – consequences for metabolism of dietary compounds and health
- ‘Omics’ provide insight into microbiota function at high resolution

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