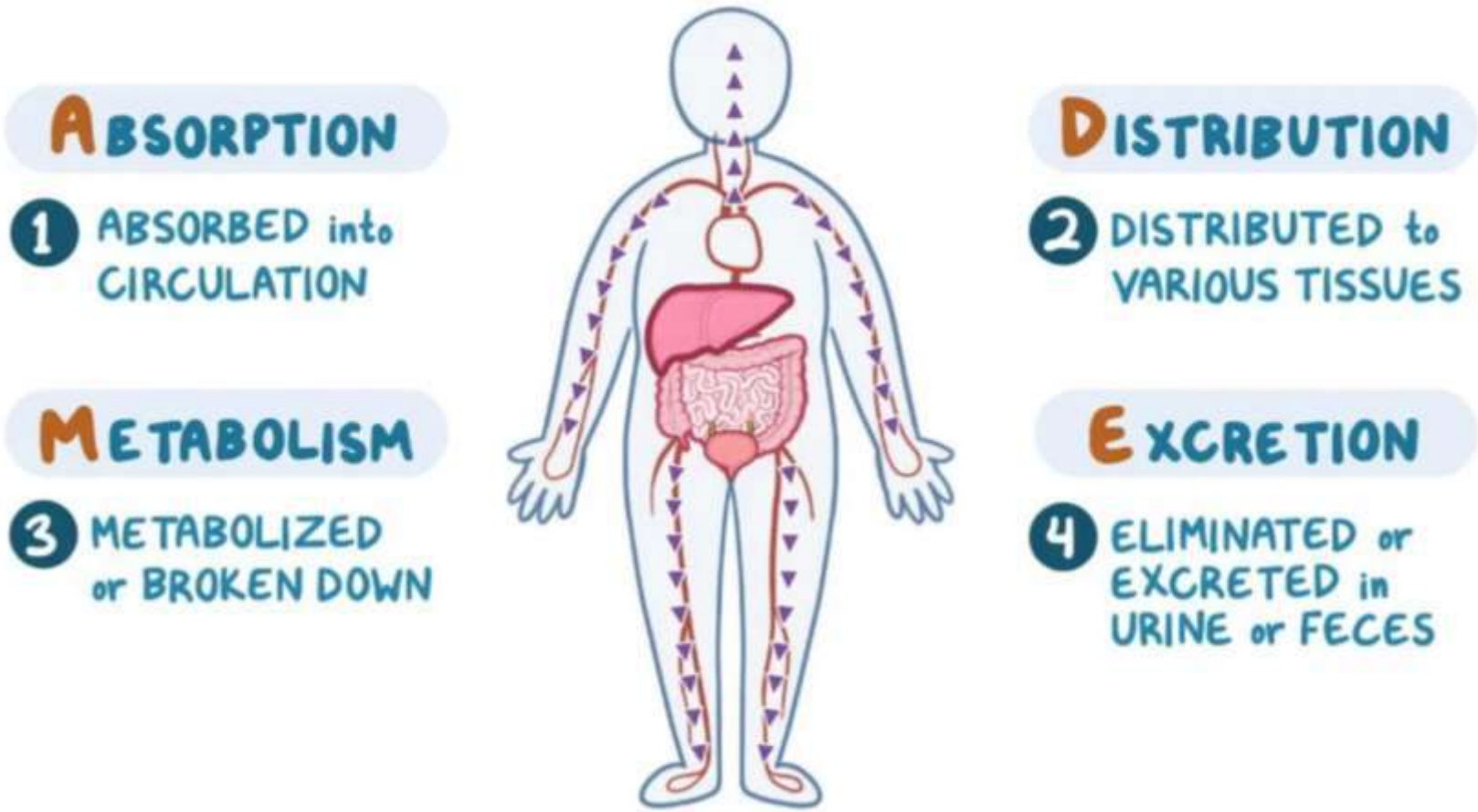
26 Novembre 2023

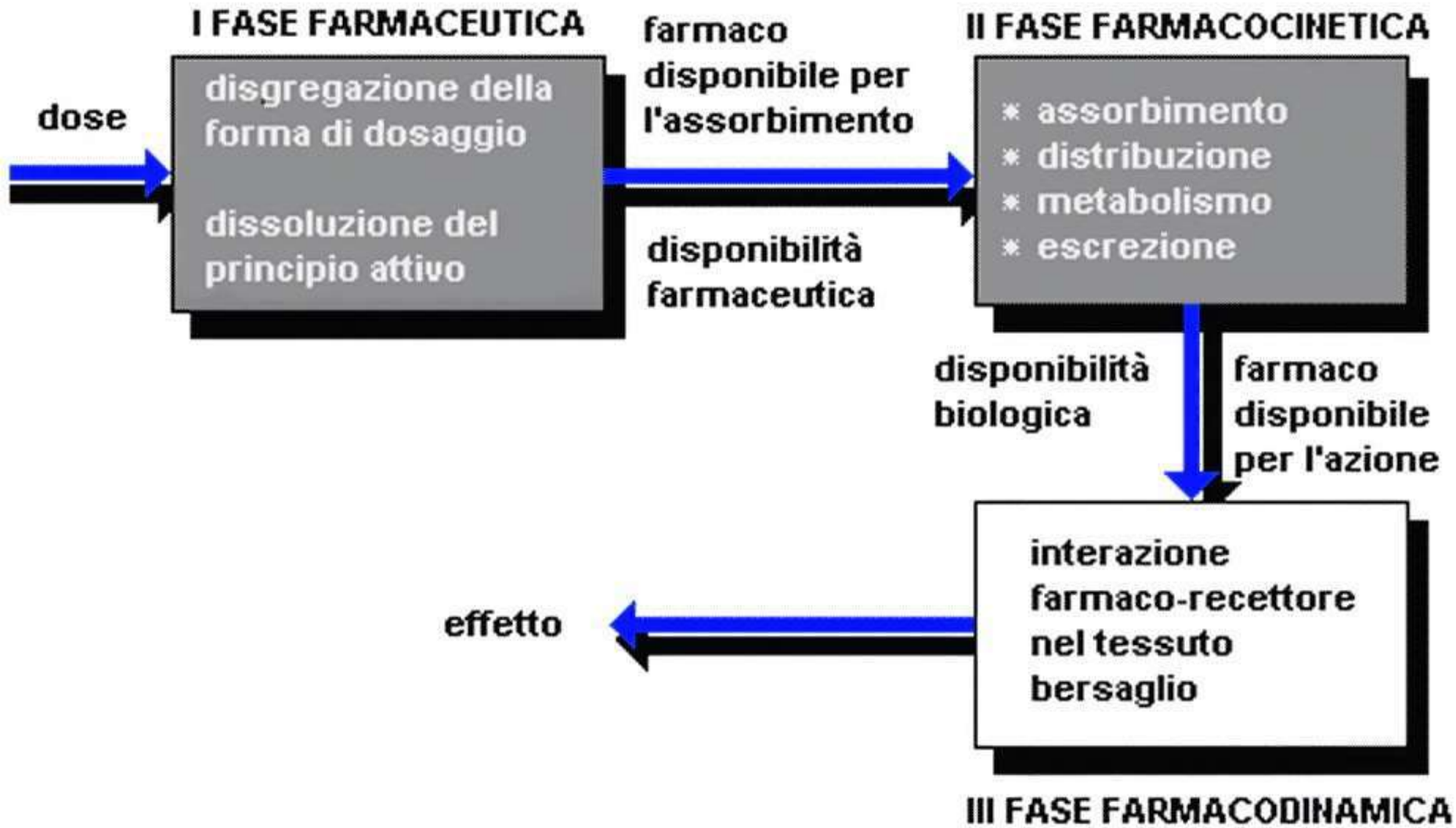
Farmacodinamica, biodisponibilità legata al benessere gastrointestinale

Prof. Stefano Dall'Acqua

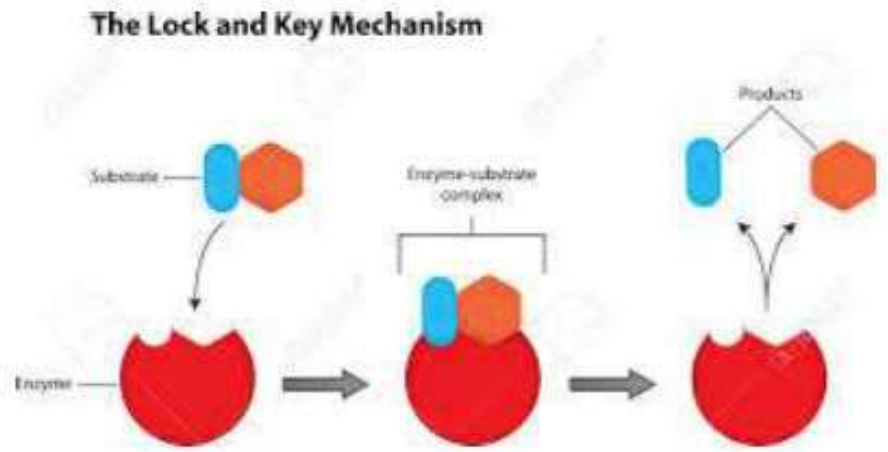
PharmD, PhD, Professore Associato Dipartimento di Scienze del Farmaco, Università degli Studi di Padova

Farmacocinetica studia l'assorbimento, la distribuzione, il metabolismo e l'eliminazione dei farmaci ADME

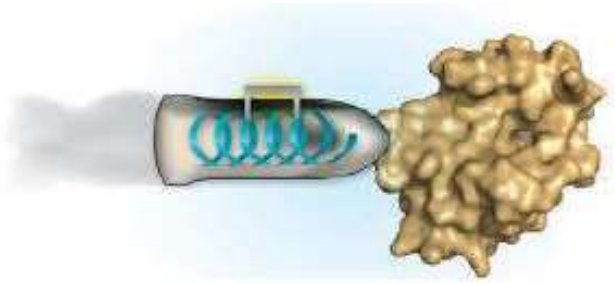



I FASE FARMACEUTICA
dose
disgregazione della forma di dosaggio
dissoluzione del principio attivo
farmaco disponibile per l'assorbimento
disponibilità farmaceutica
II FASE FARMACOCINETICA
* assorbimento
* distribuzione
* metabolismo
* escrezione
disponibilità biologica
farmaco disponibile per l'azione
interazione farmaco-recettore nel tessuto bersaglio
effetto
III FASE FARMACODINAMICA

MECCANISMI D'AZIONE …

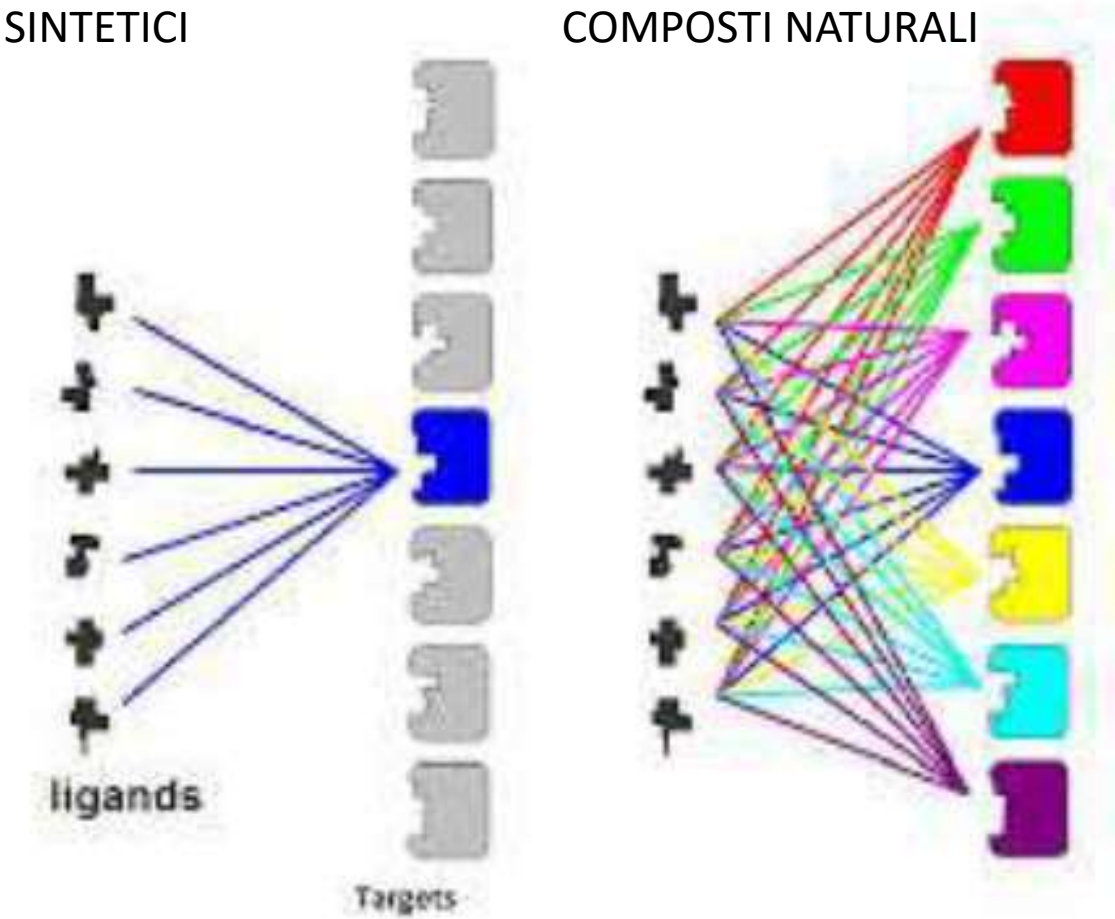


Un composto che colpisce uno specifico bersaglio



COMPOSTI SINTETICI

COMPOSTI NATURALI



MISCELA DI COMPOSTI → **AZIONE MULTI-TARGET**

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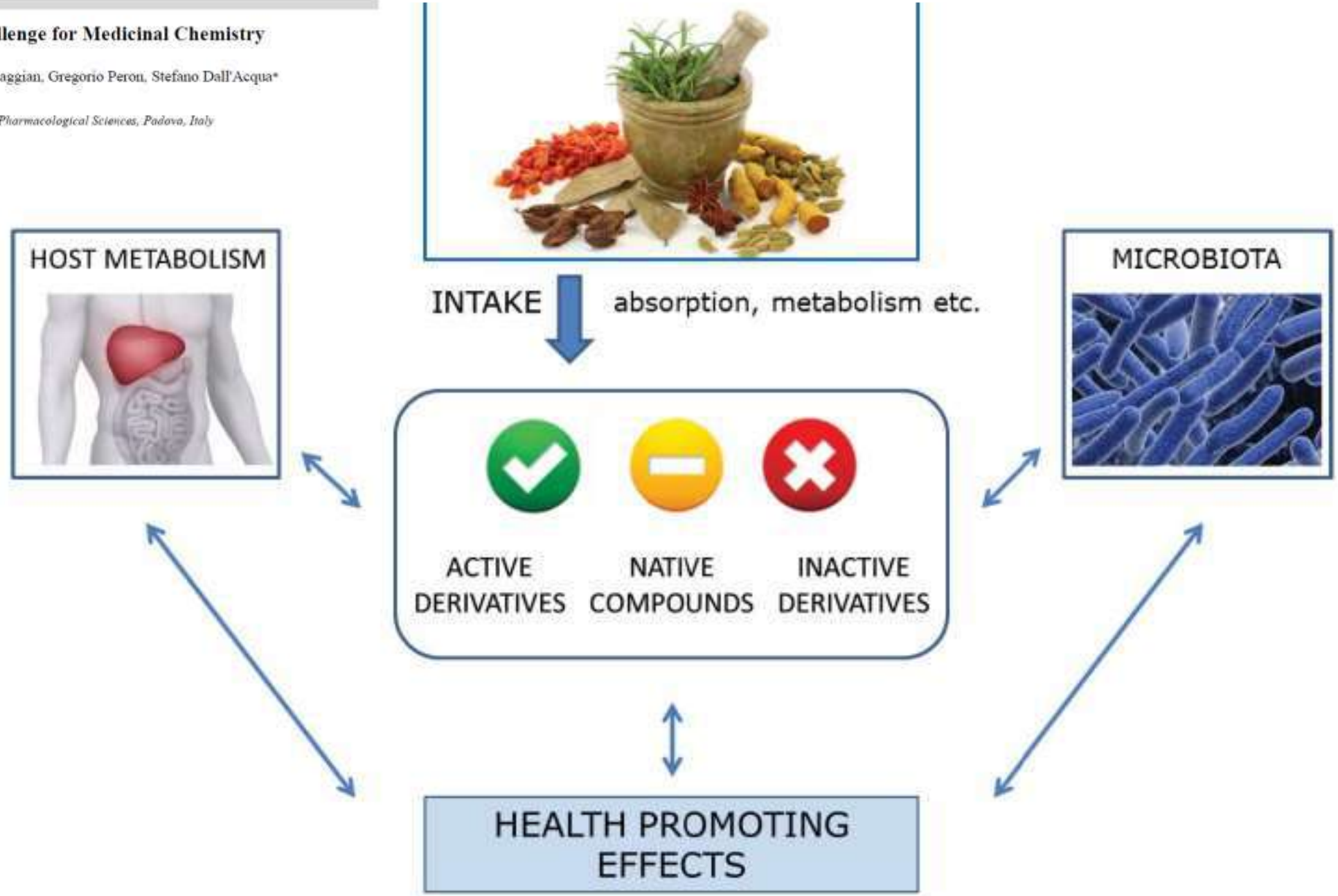
Current Medicinal Chemistry, 2016, *23*, 1-26

REVIEW ARTICLE

Nutraceuticals, a New Challenge for Medicinal Chemistry

Stefania Sut, Valeria Baldan, Marta Faggian, Gregorio Peron, Stefano Dall'Acqua*

University of Padova - Pharmaceutical and Pharmacological Sciences, Padova, Italy



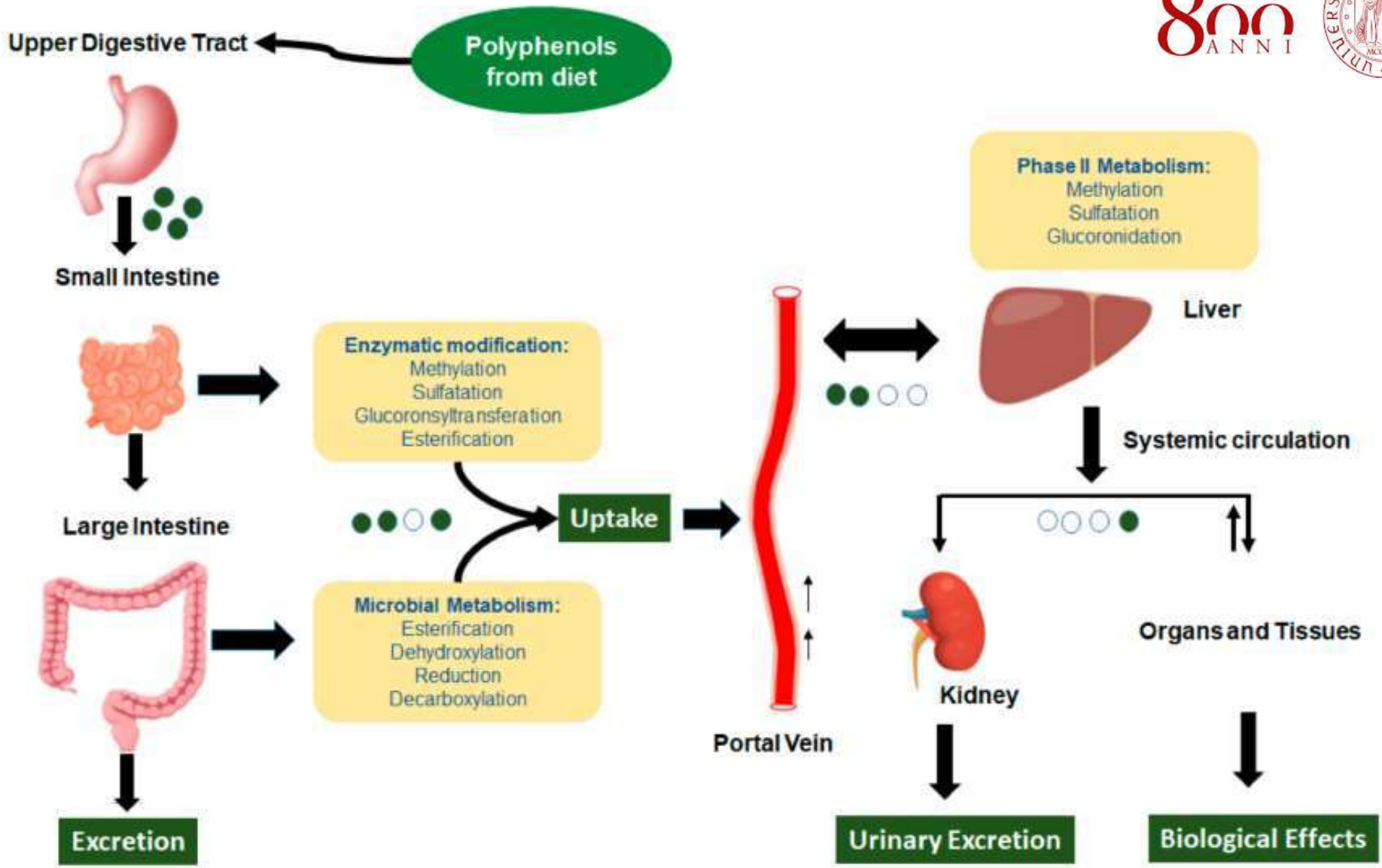
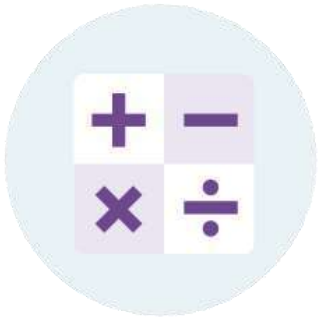


Figure 2. Schematic representation of the absorption and metabolism of dietary polyphenols. Green dots represent aglycon polyphenols, and white dots represent their metabolites.

Quanto sono biodisponibili i composti naturali in generale?

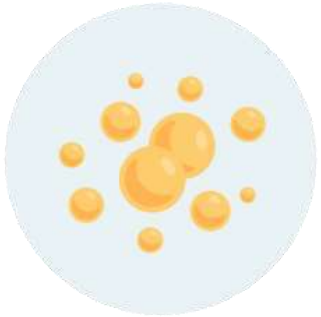
Fattori che influenzano la biodisponibilità di un composto

Processing
(heat, drying)

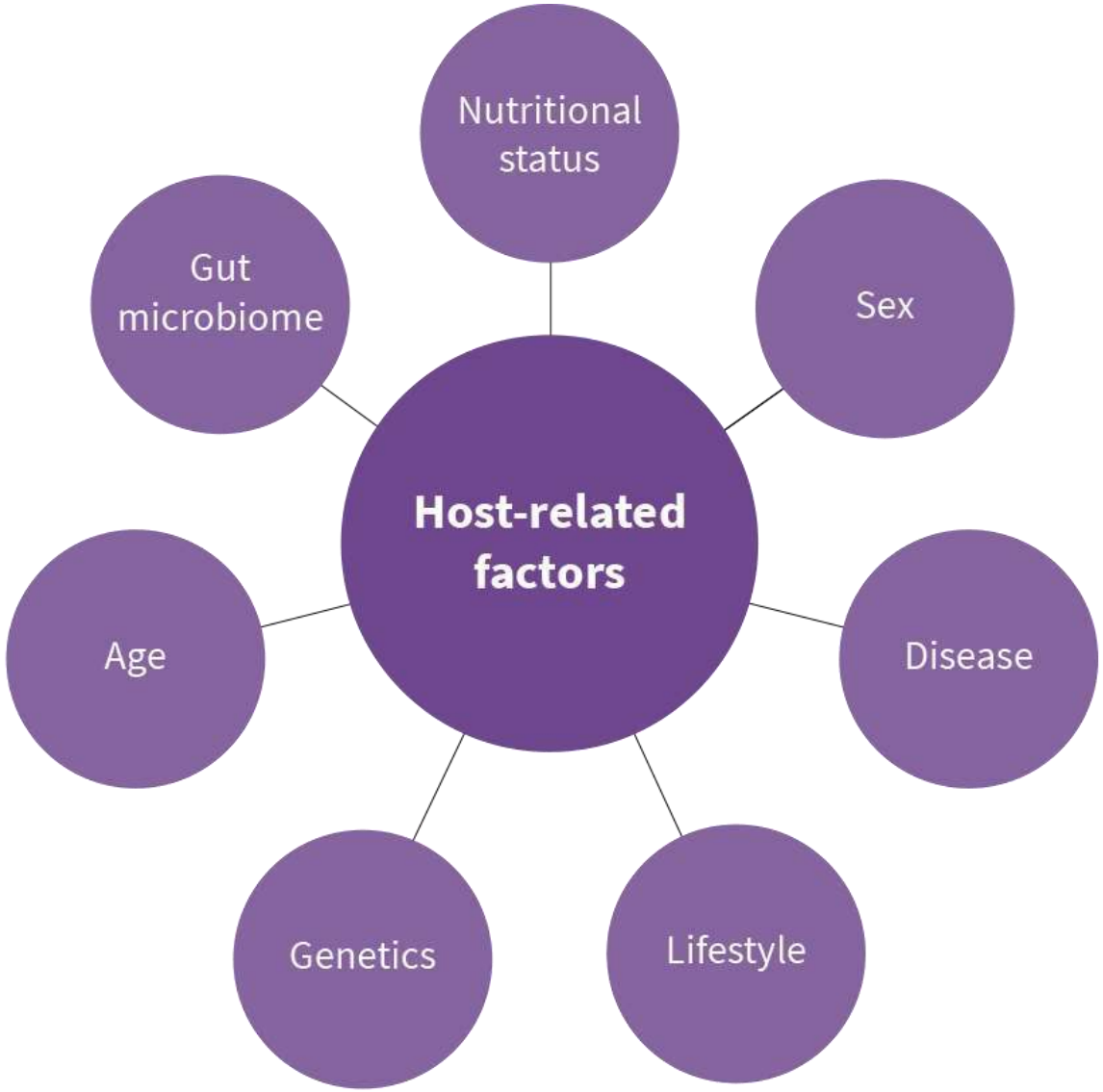


Intake
(dosing, co-ingestion, interactions)

Source
(liquid vs solid, food matrix, encapsulation)



Lipid Presence



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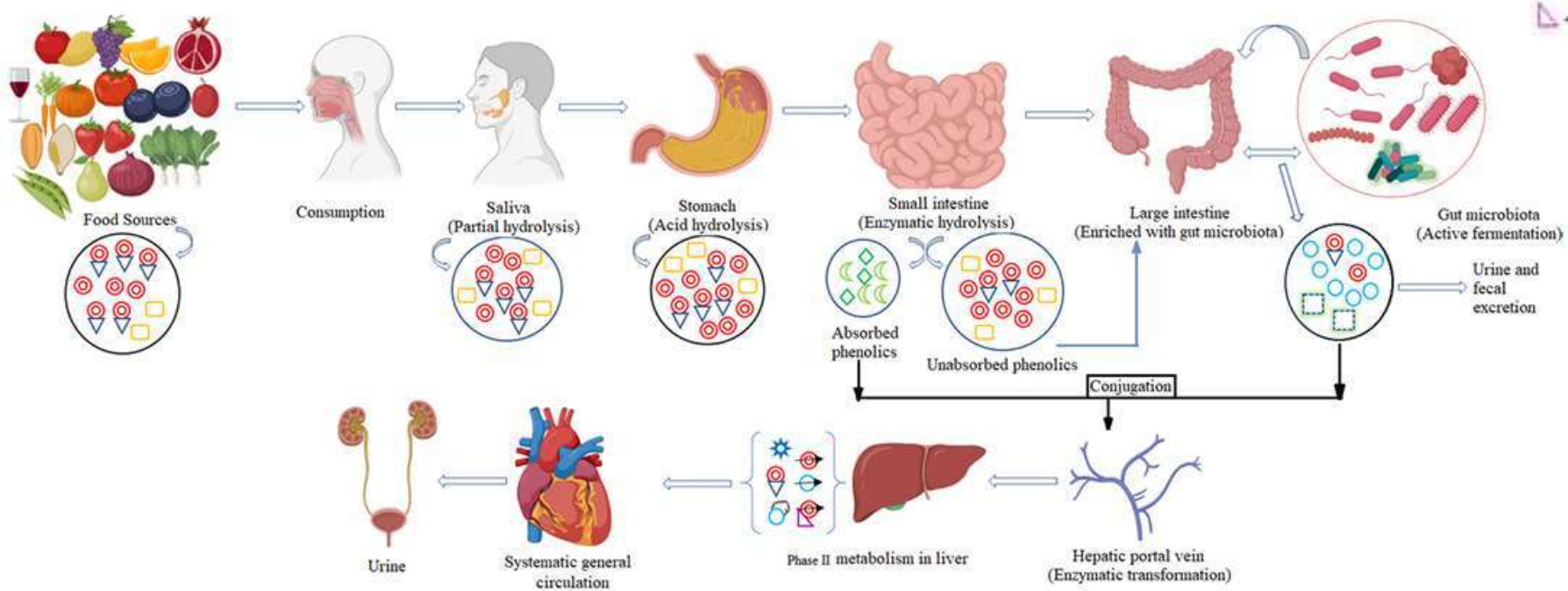
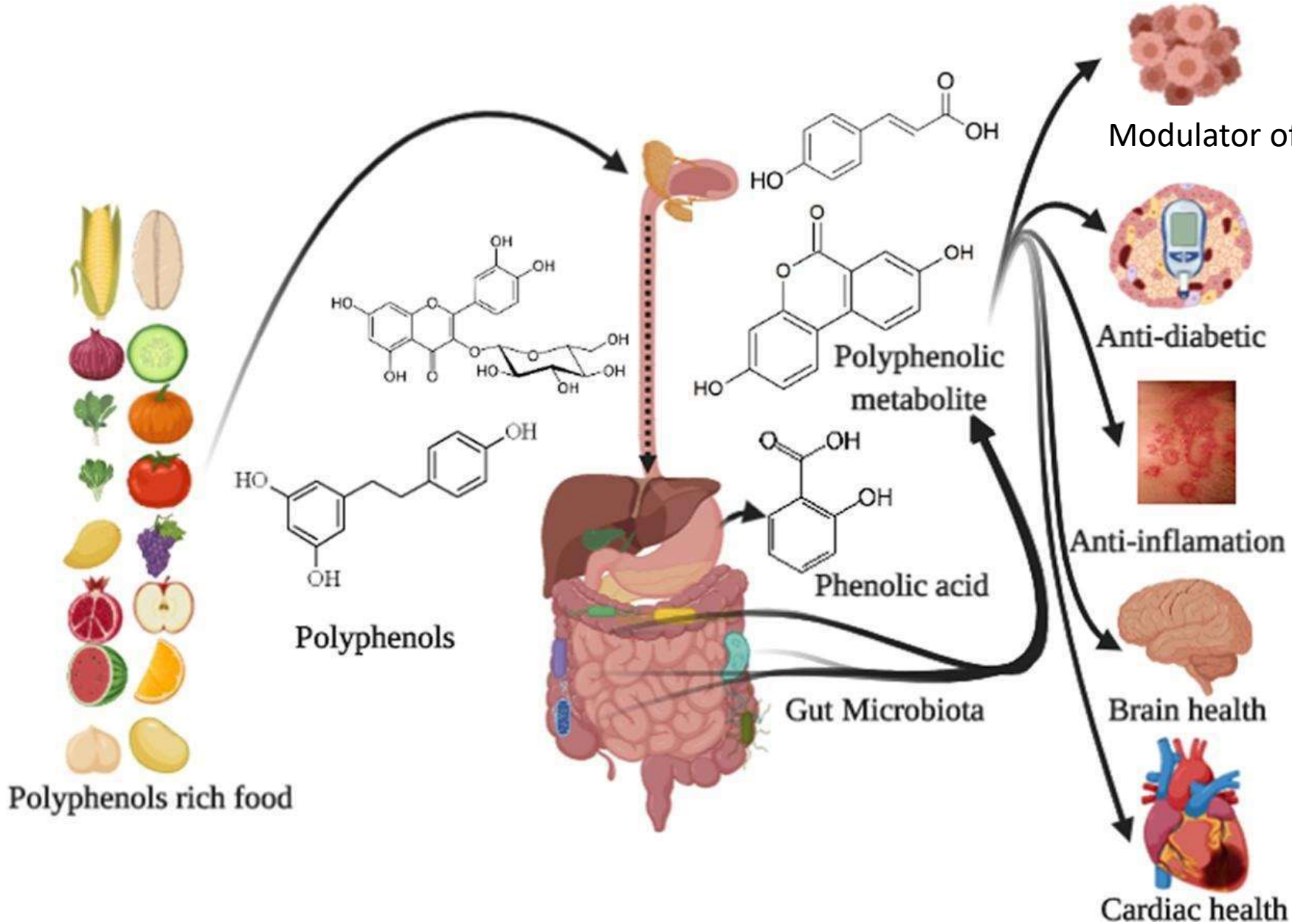
Review

Role of dietary polyphenols on gut microbiota, their metabolites and health benefits

S. Mithul Aravind [a], Santad Wichienchot [b], Rong Tsao [c,*], S. Ramakrishnan [d], S. Chakkaravarthi [a,*]




Modulator of cell grow
Anti-diabetic
Anti-inflamation
Brain health
Cardiac health
Polyphenolic metabolite
Phenolic acid
Gut Microbiota
Polyphenols
Polyphenols rich food

Strategie per l'incremento dell'assorbimento dei polifenoli

Poco idrosolubili : aggiungere tensioattivi (lecitine, tween etc)
Ridurre azione di glucuronidasi (piperina) per aumentare emivita
Piperina inibisce trasportatori (Pgp) che riducono assorbimento
Enhancer: NAC
Nanoformulazioni
Formulazione in liposomi, Fitosomi etc
Somministrazione con grassi per composti liposolubili
Micronizzazioni

Co-macinazione e formazione di emulsioni solide
Natural Deep Eutectic Solvents

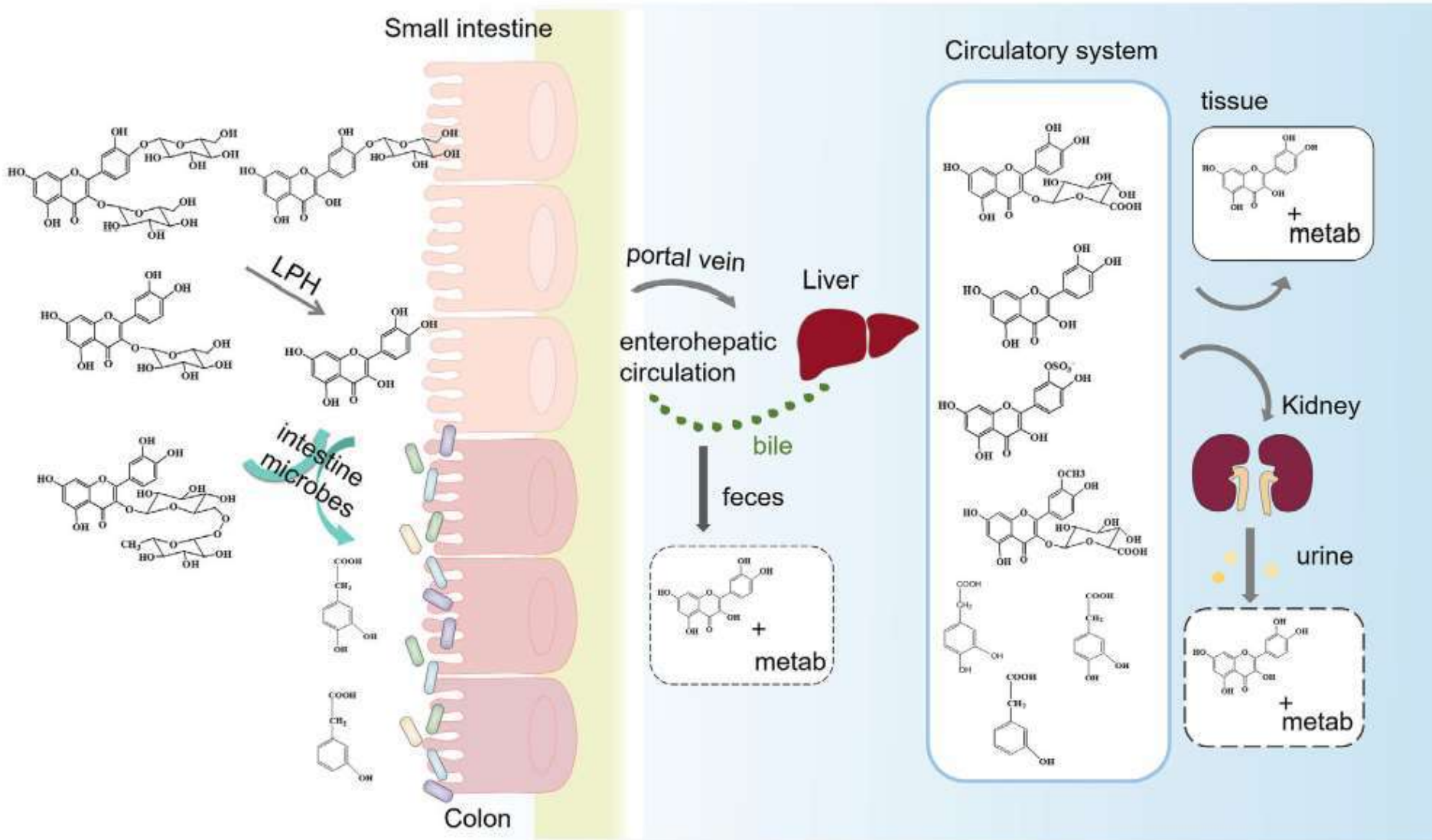
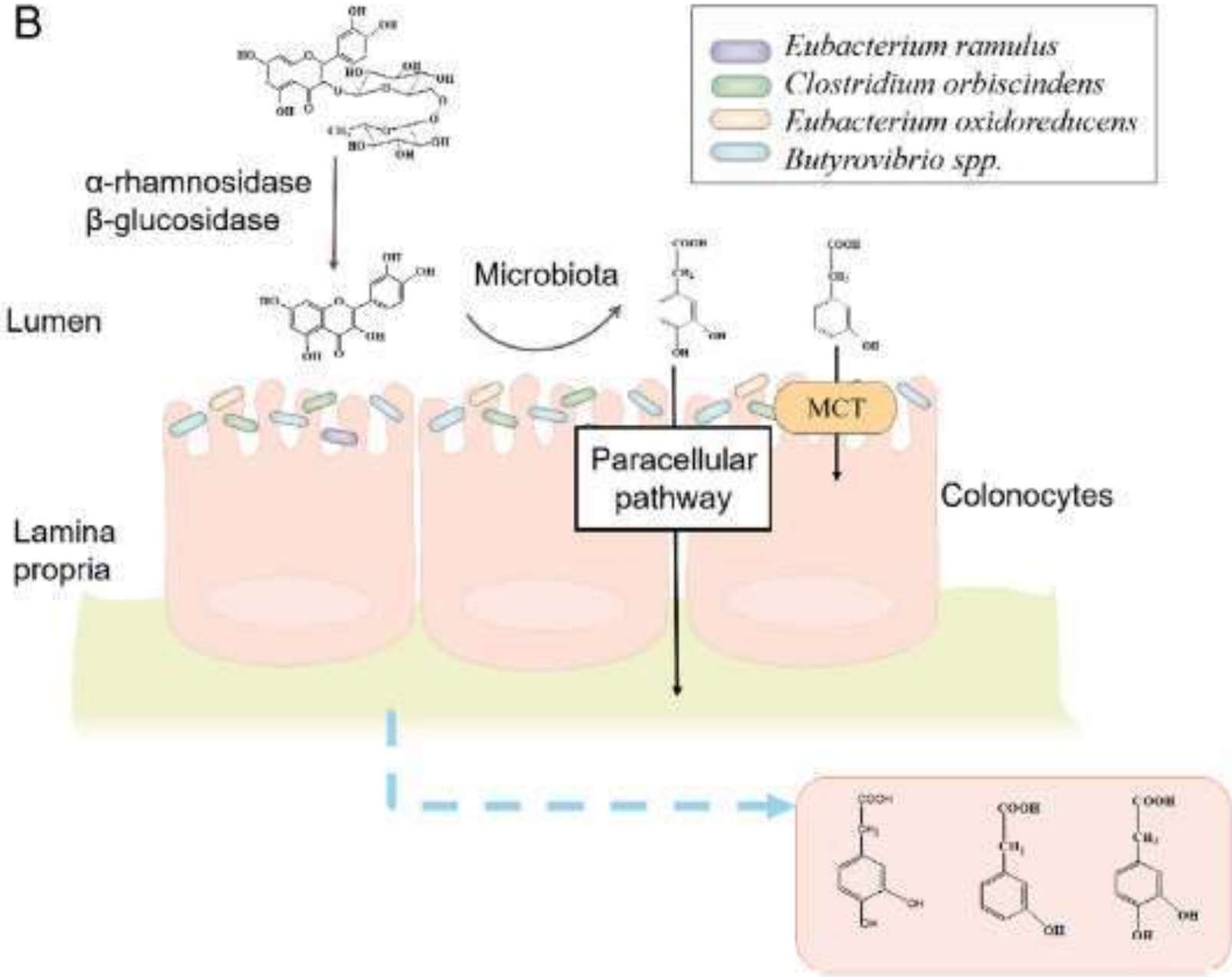
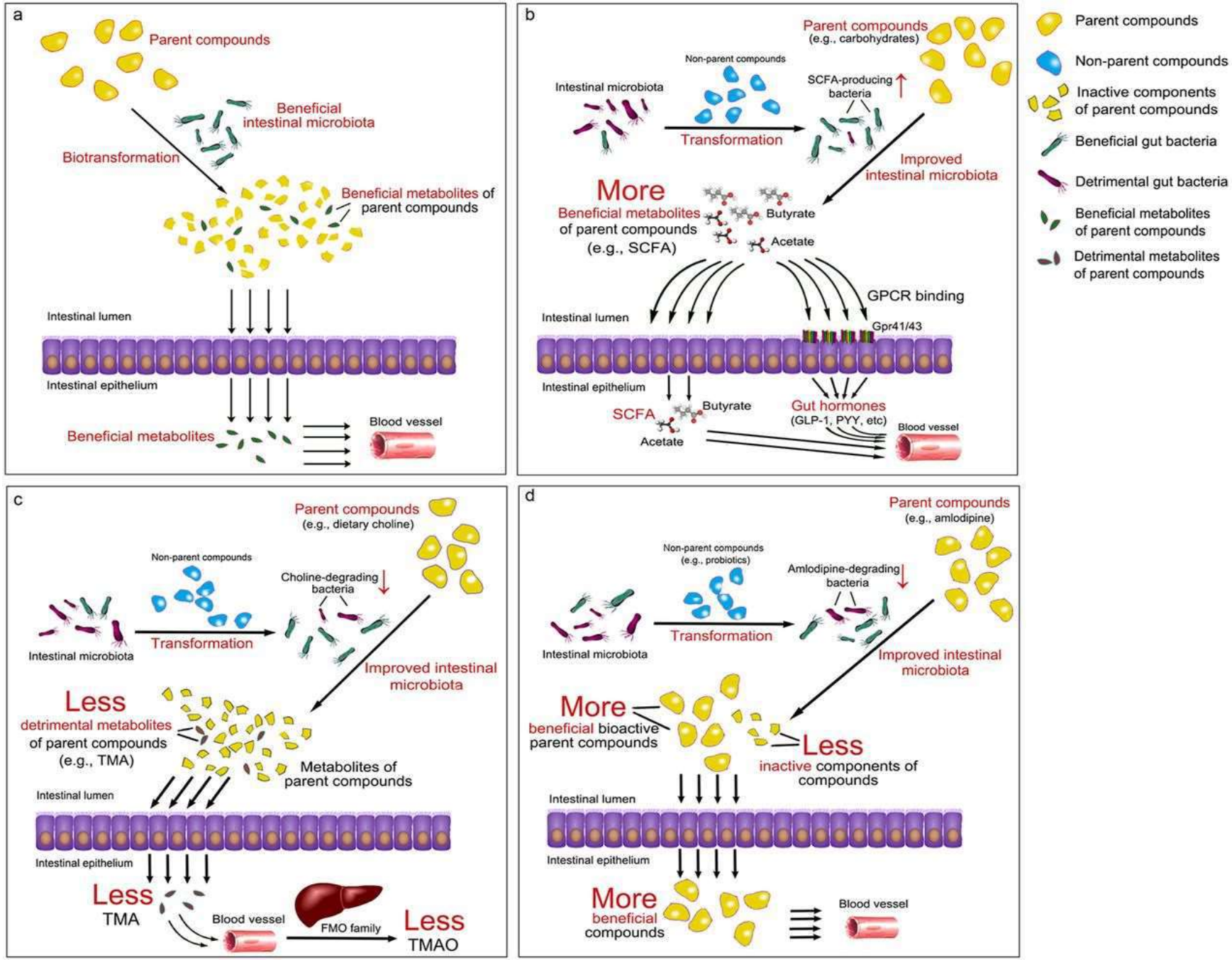


FIGURE 1 Schematic representation of processes of quercetin absorption metabolism and elimination *in vivo*. *Abbreviations*: LPH, lactasephlorizin hydrolase


B
Eubacterium ramulus
Clostridium orbiscindens
Eubacterium oxidoreducens
Butyrovibrio spp.
α-rhamnosidase
β-glucosidase
Microbiota
Lumen
MCT
Paracellular pathway
Colonocytes
Lamina propria


a
Parent compounds
Beneficial intestinal microbiota
Biotransformation
Beneficial metabolites of parent compounds
Intestinal lumen
Intestinal epithelium
Beneficial metabolites
Blood vessel
b
Parent compounds (e.g., carbohydrates)
Non-parent compounds
Intestinal microbiota
SCFA-producing bacteria
Transformation
Improved intestinal microbiota
More
Beneficial metabolites of parent compounds (e.g., SCFA)
Butyrate
Acetate
GPCR binding
Intestinal lumen
Gpr41/43
Intestinal epithelium
SCFA
Butyrate
Acetate
Gut hormones (GLP-1, PYY, etc)
Blood vessel
c
Parent compounds (e.g., dietary choline)
Non-parent compounds
Choline-degrading bacteria
Intestinal microbiota
Transformation
Improved intestinal microbiota
Less
detrimental metabolites of parent compounds (e.g., TMA)
Metabolites of parent compounds
Intestinal lumen
Intestinal epithelium
Less
TMA
Blood vessel
FMO family
Less
TMAO
d
Parent compounds (e.g., amlodipine)
Non-parent compounds (e.g., probiotics)
Amlodipine-degrading bacteria
Intestinal microbiota
Transformation
Improved intestinal microbiota
More
beneficial bioactive parent compounds
Less
inactive components of compounds
Intestinal lumen
Intestinal epithelium
More
beneficial compounds
Blood vessel
Parent compounds
Non-parent compounds
Inactive components of parent compounds
Beneficial gut bacteria
Detrimental gut bacteria
Beneficial metabolites of parent compounds
Detrimental metabolites of parent compounds

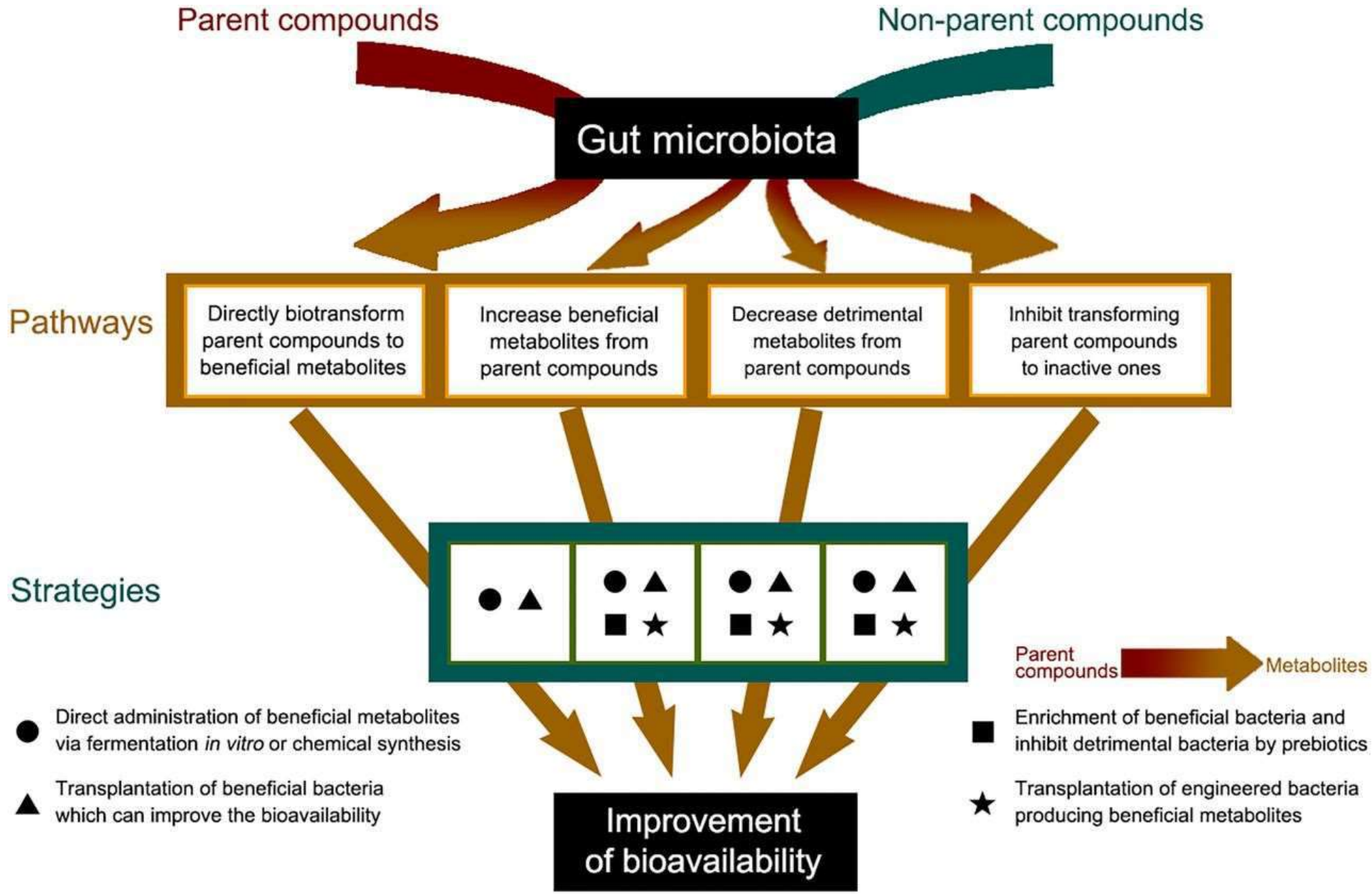
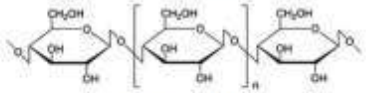
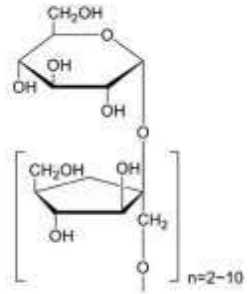
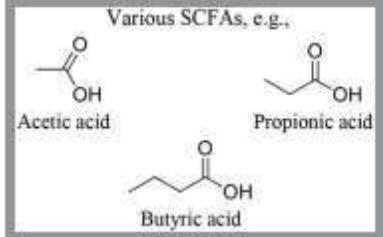
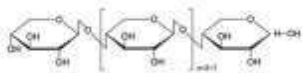
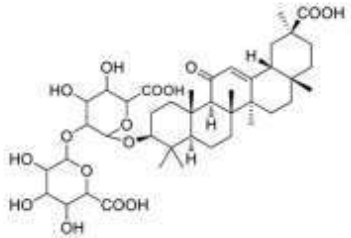
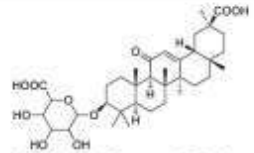
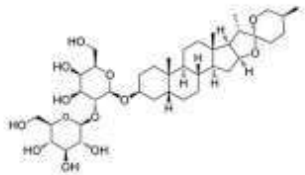
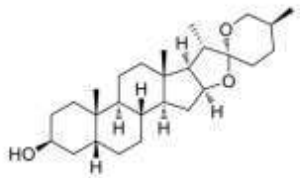
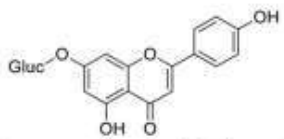
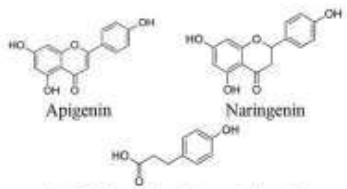
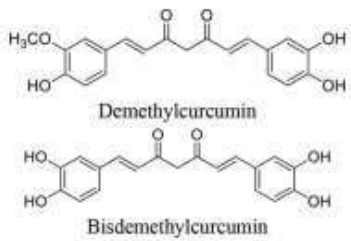

Parent compounds
Non-parent compounds
Gut microbiota
Pathways
Directly biotransform parent compounds to beneficial metabolites
Increase beneficial metabolites from parent compounds
Decrease detrimental metabolites from parent compounds
Inhibit transforming parent compounds to inactive ones
Strategies
Parent compounds
Metabolites
Direct administration of beneficial metabolites via fermentation *in vitro* or chemical synthesis
Transplantation of beneficial bacteria which can improve the bioavailability
Enrichment of beneficial bacteria and inhibit detrimental bacteria by prebiotics
Transplantation of engineered bacteria producing beneficial metabolites
Improvement of bioavailability

TABLE 1 Participants involved in the four pathways to improve bioavailability

Pathway 1: direct biotransformation of parent compounds to beneficial metabolites by the gut microbiota				
Parent compound	**Metabolite(s) of parent compound**	**Gut bacterium(a)**	**Function(s)**	**Reference(s)**
 Dietary fiber		*Faecalibacterium prausnitzii*, *Bifidobacterium* spp., *Lactobacillus* spp.	Alleviation of T2DM	18
Ganoderma atrum polysaccharides		S24-7, SMB53, Rc4-4, *Rikenellaceae*, *Allobaculum*, *Ruminococcaceae*	Promotion of secretory immunoglobulin A in the intestine	62, 64
Polygonatum odoratum polysaccharides		*Ruminococcus* spp., *Prevotella* spp.	Alleviation of hyperglycemia, hyperlipidemia, and obesity	60
Cordyceps sinensis polysaccharides		Unidentified gut bacteria	Enhancement of immune function of mesenteric lymph node lymphocytes and promotion of proliferation and inhibition of apoptosis of intestinal epithelial cells	62
 Fructo-oligosaccharide (FOS)	 Various SCFAs, e.g., Acetic acid, Propionic acid, Butyric acid	*Lactobacillus* spp., *Bifidobacterium* spp.	Decrease of ghrelin, glucose, and insulin levels; enhancement of peptide YY levels	65, 69
 Xylooligosaccharide (XOS)		*Bifidobacterium* spp.	Alleviation of chronic kidney disease and ulcerative colitis	70–72

 Glycyrrhizin (GL)	 Glycyrrhetic acid 3-O-mono-β-D-glucuronide (GAMG)	*Eubacterium* sp. GLH, *Ruminococcus* sp. PO1-3, *Clostridium innocuum* ES24-06	Improvement of anti-inflammatory, antiviral, antioxidative, and anticancer effects	95–97
 Timosaponin AIII (TA)	 Sarsasapogenin (SG)	Unidentified gut bacteria	Anti-inflammatory effect	84
 Flavone apigenin-7-glucoside (A7G)	 Apigenin Naringenin 3-(4-Hydroxyphenyl) propionic acid	*Enterococcus avium*, *Clostridium orbiscindens*, *Eubacterium ramulus*, *Bacteroides distasonis*	Antimutagenic, antiproliferative, and antiallergic effects	102
 Curcumin	 Demethylcurcumin Bisdemethylcurcumin	*Blautia* spp.	Anti-inflammatory, antioxidant, antimutagenic, and anticancer effects	7, 113

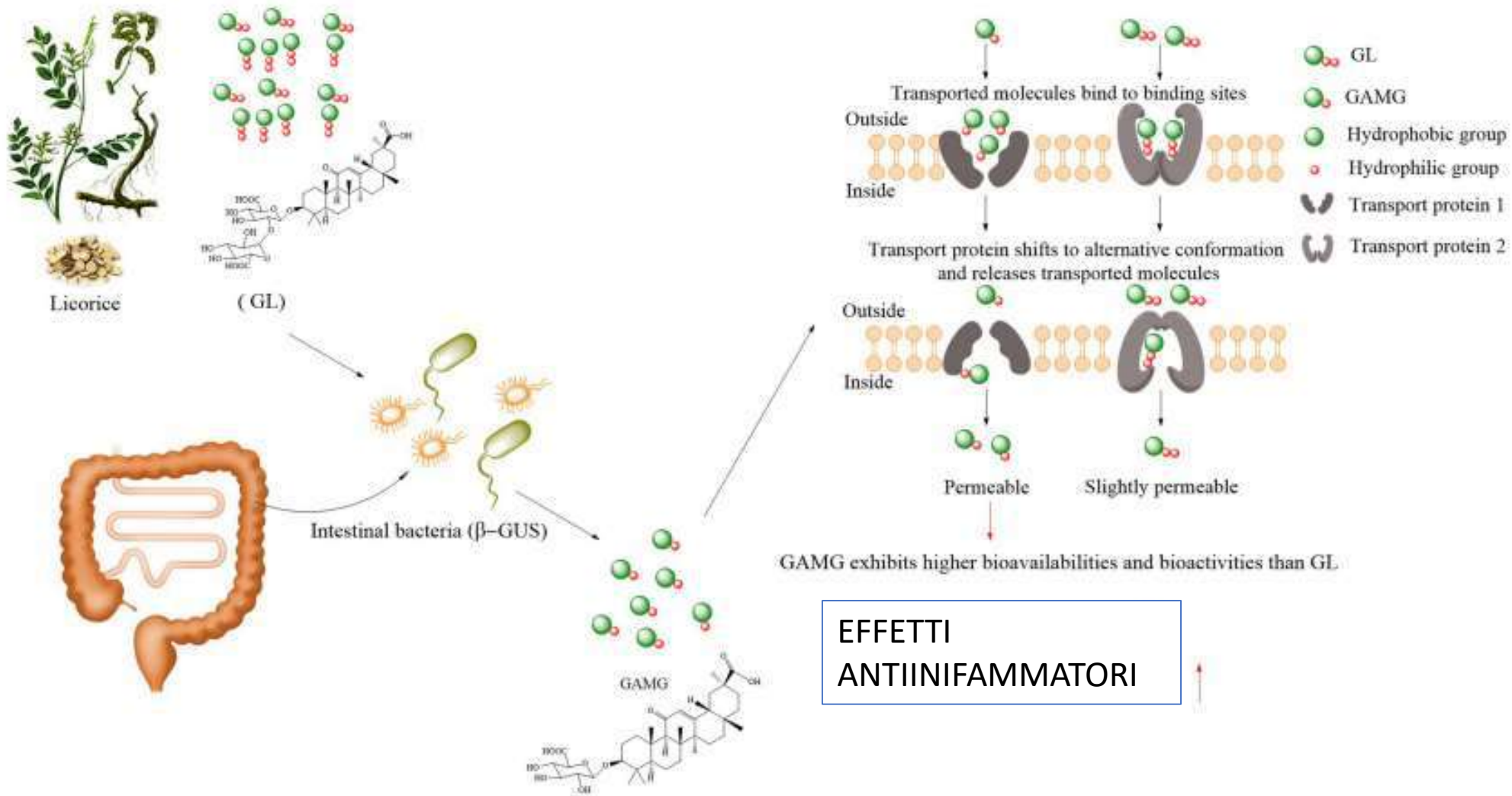
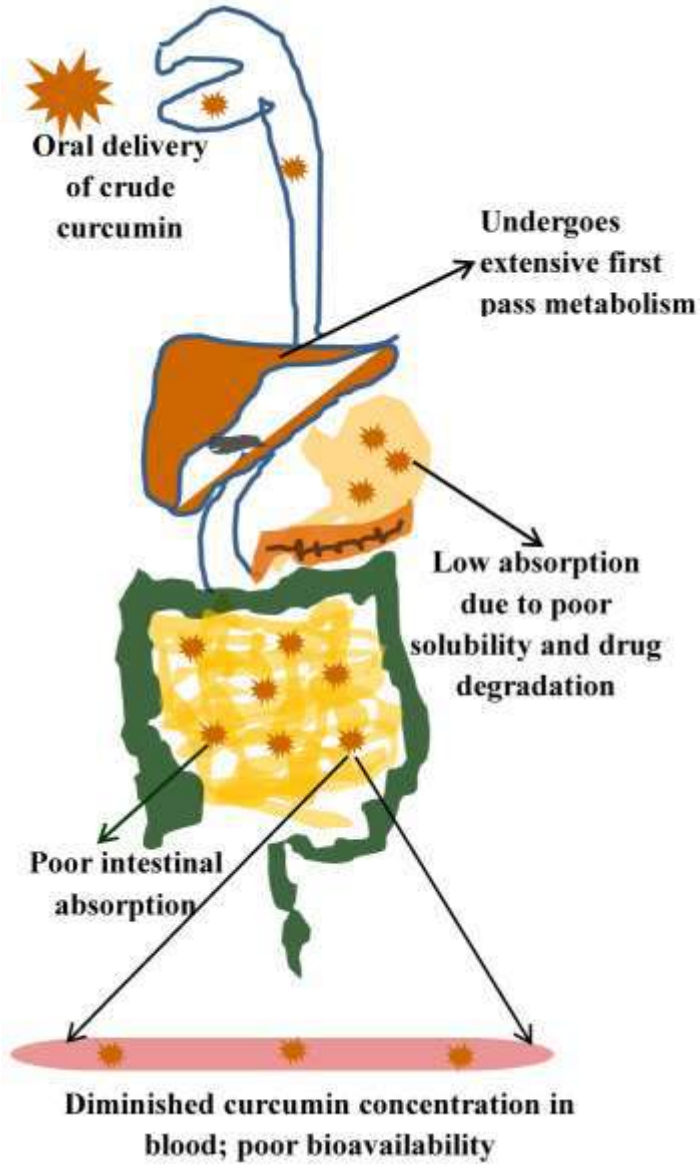
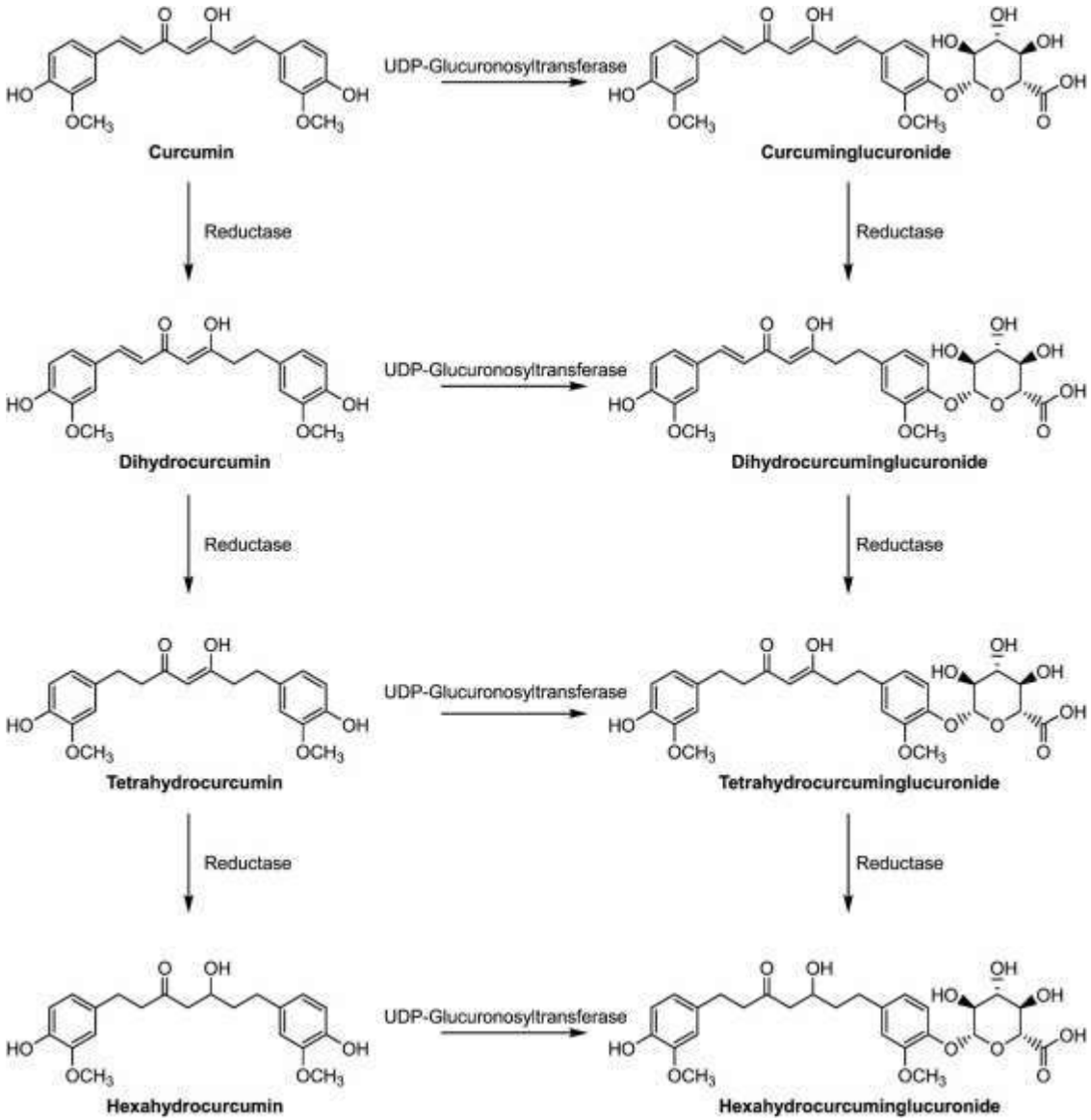
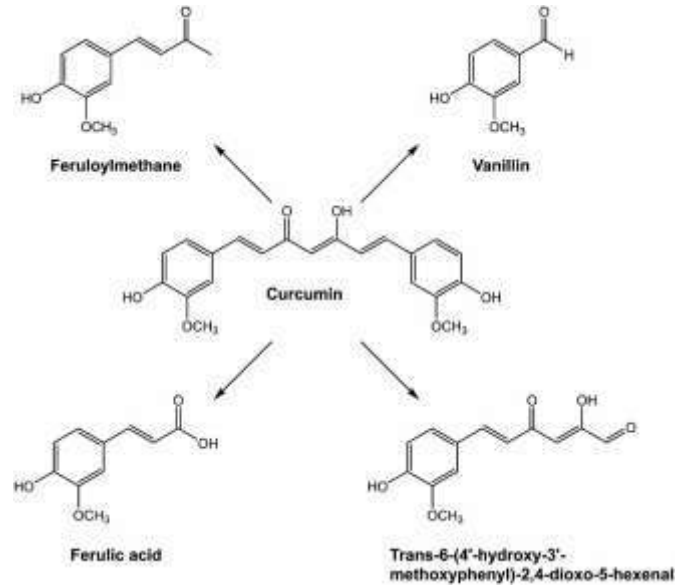


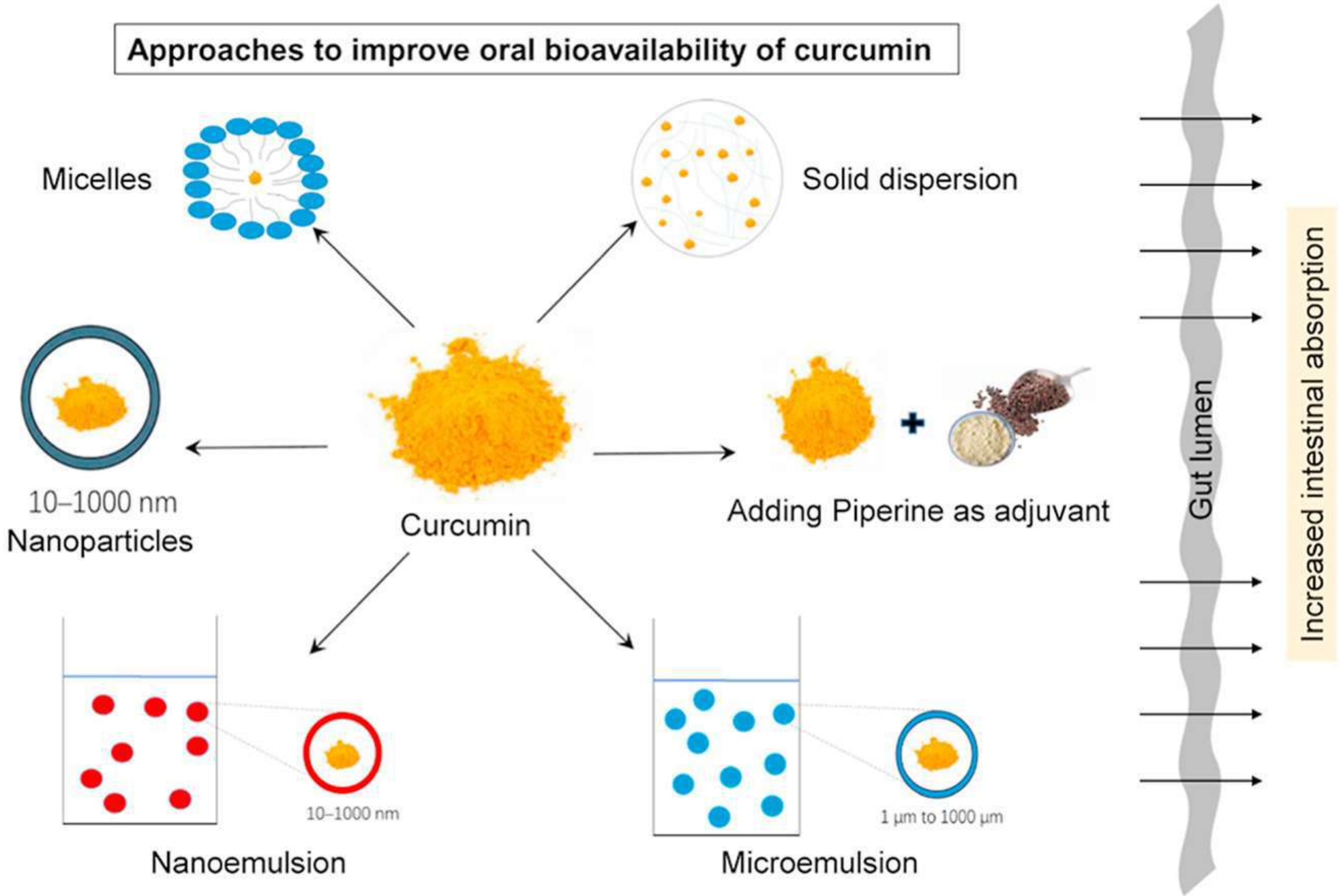
FIG 3 Representative example with a promising application of pathway 1: metabolism of a parent compound (glycyrrhizin, for example) into value-added compounds by regulation of the gut microbiota.

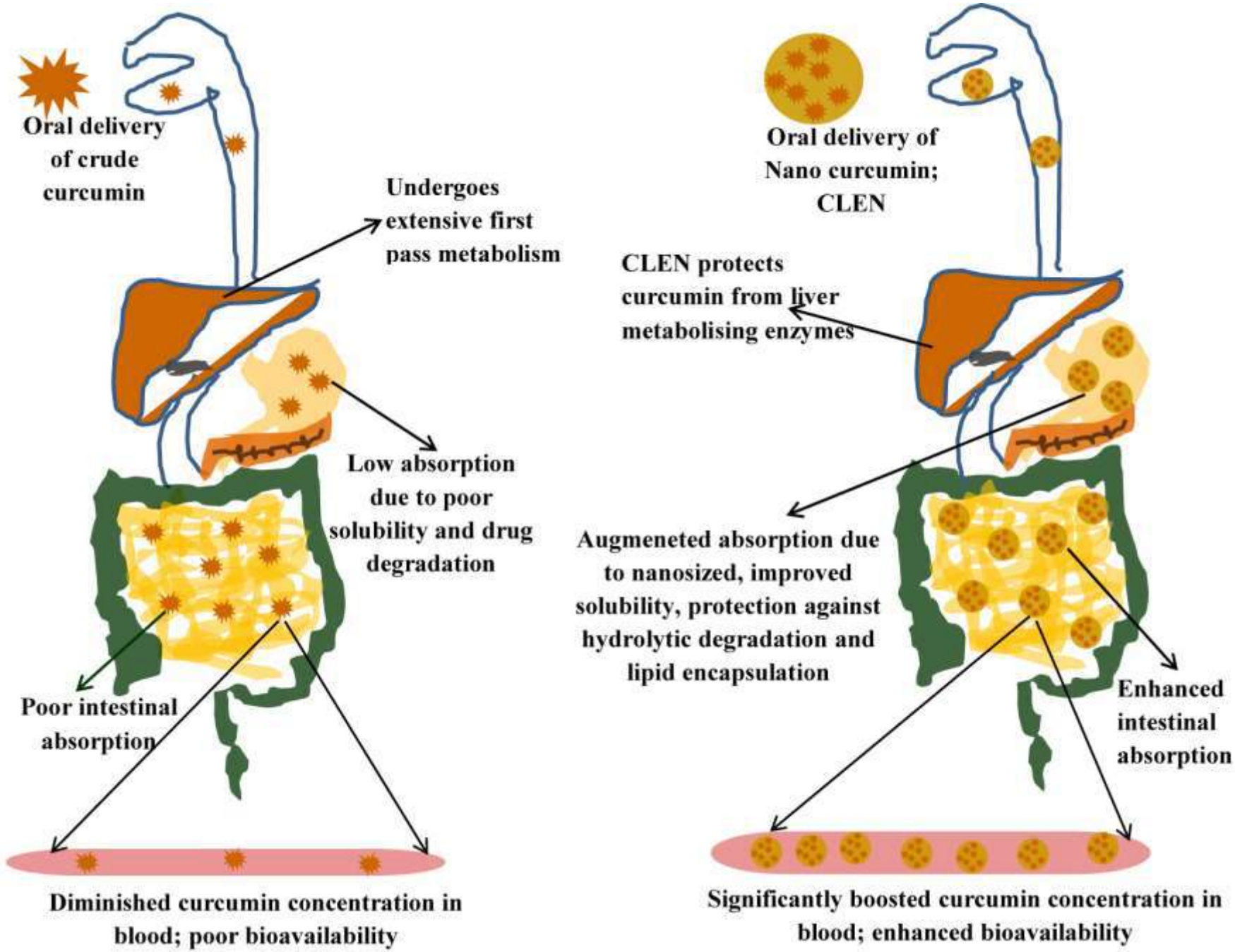
6b.

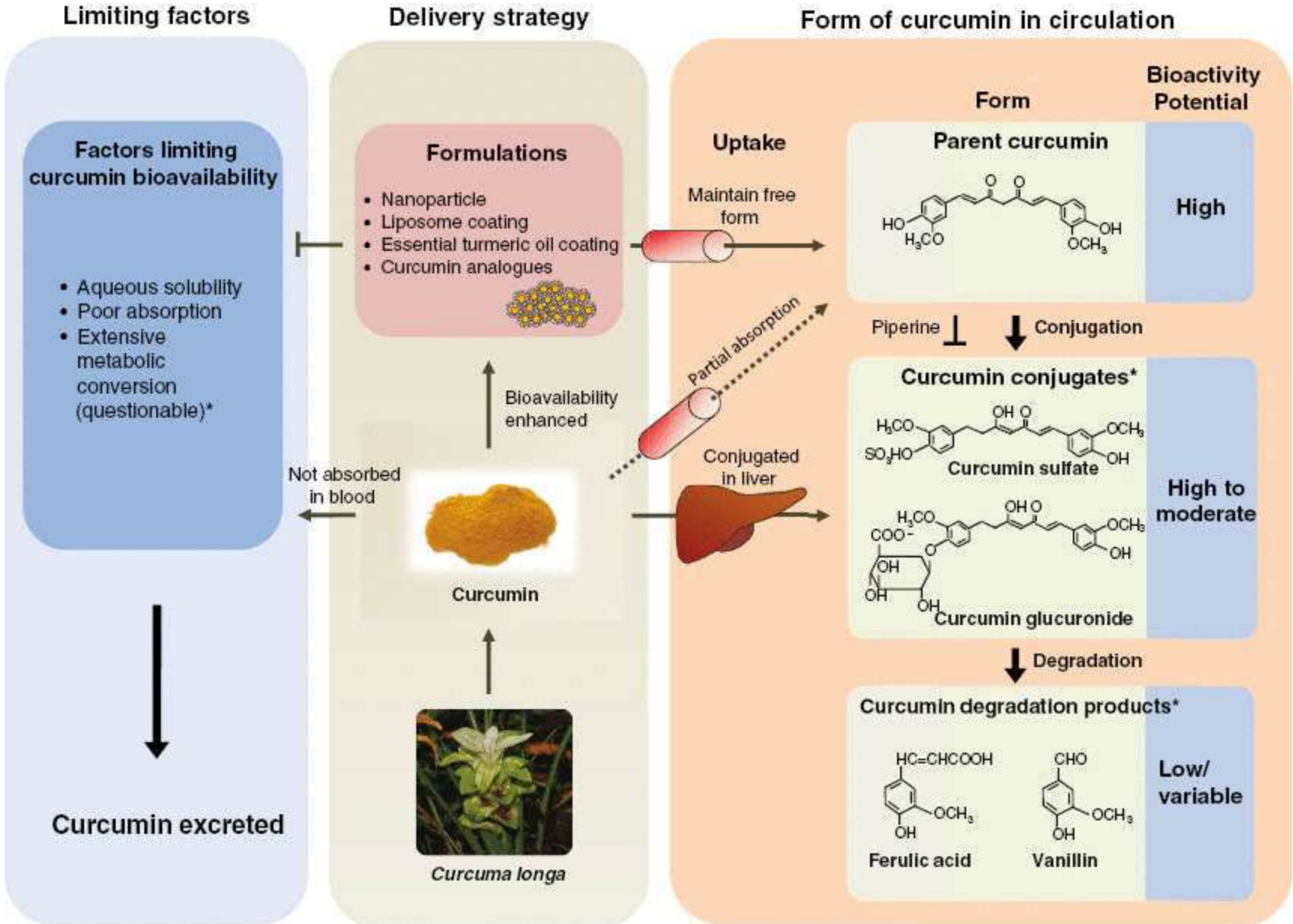

Oral delivery of crude curcumin
Undergoes extensive first pass metabolism
Low absorption due to poor solubility and drug degradation
Poor intestinal absorption
Diminished curcumin concentration in blood; poor bioavailability


Curcumin
UDP-Glucuronosyltransferase
Curcuminglucuronide
Reductase
Reductase
Dihydrocurcumin
UDP-Glucuronosyltransferase
Dihydrocurcuminglucuronide
Reductase
Reductase
Tetrahydrocurcumin
UDP-Glucuronosyltransferase
Tetrahydrocurcuminglucuronide
Reductase
Reductase
Hexahydrocurcumin
UDP-Glucuronosyltransferase
Hexahydrocurcuminglucuronide


Feruloylmethane
Vanillin
Curcumin
Ferulic acid
Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal


Approaches to improve oral bioavailability of curcumin
Micelles
Solid dispersion
10–1000 nm
Nanoparticles
Curcumin
Adding Piperine as adjuvant
Gut lumen
Increased intestinal absorption
10–1000 nm
Nanoemulsion
1 μm to 1000 μm
Microemulsion


Oral delivery of crude curcumin
Undergoes extensive first pass metabolism
Low absorption due to poor solubility and drug degradation
Poor intestinal absorption
Diminished curcumin concentration in blood; poor bioavailability
Oral delivery of Nano curcumin; CLEN
CLEN protects curcumin from liver metabolising enzymes
Augmeneted absorption due to nanosized, improved solubility, protection against hydrolytic degradation and lipid encapsulation
Enhanced intestinal absorption
Significantly boosted curcumin concentration in blood; enhanced bioavailability


Limiting factors
Delivery strategy
Form of curcumin in circulation
Factors limiting curcumin bioavailability
• Aqueous solubility
• Poor absorption
• Extensive metabolic conversion (questionable)*
Curcumin excreted
Formulations
• Nanoparticle
• Liposome coating
• Essential turmeric oil coating
• Curcumin analogues
Bioavailability enhanced
Not absorbed in blood
Curcumin
Curcuma longa
Uptake
Maintain free form
Partial absorption
Conjugated in liver
Form
Bioactivity Potential
Parent curcumin
High
Piperine
Conjugation
Curcumin conjugates*
Curcumin sulfate
Curcumin glucuronide
High to moderate
Degradation
Curcumin degradation products*
Ferulic acid
Vanillin
Low/ variable

The FEBS Journal

FEBS PRESS science publishing by scientists

Biochemical and cellular mechanism of protein kinase CK2 inhibition by deceptive curcumin

Giorgio Cozza[1], Francesca Zonta[2], Andrea Dalle Vedove[3], Andrea Venerando[4], Stefano Dall'Acqua[5], Roberto Battistutta[6,7], Maria Ruzzene[2] and Graziano Lolli[3]

Curcumin in vivo is degradated to some minor phenolic compounds

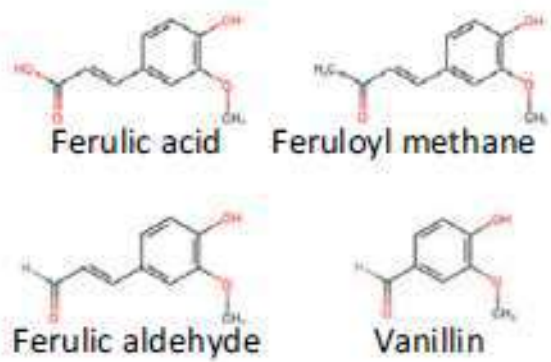


Table 1. IC_{50} values of curcumin and derivatives for CK2 $\alpha_2\beta_2$ at different incubation times (min). Values represent the mean and SD of five independent experiments.

Compound	IC_{50} (μM) t = 30 min	IC_{50} (μM) t = 25 min	IC_{50} (μM) t = 20 min	IC_{50} (μM) t = 15 min	IC_{50} (μM) t = 5 min
Ferulic Acid	0.84 ± 0.10 (Ki = 0.41)			0.81 ± 0.08	0.87 ± 0.05
Ferulic aldehyde	40.1 ± 1.81			40.9 ± 1.94	40.6 ± 2.21
Feruloylmethane	65.5 ± 3.26			68.6 ± 4.15	61.8 ± 3.22
Vanillin	53.4 ± 2.91			52.2 ± 1.87	57.6 ± 2.32
Curcumin	2.38 ± 0.15	2.32 ± 0.11	3.2 ± 0.5	10.8 ± 0.64	85.1 ± 3.11
Quinalizarin	0.11 ± 0.03			0.15 ± 0.04	0.13 ± 0.02

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These compounds can act as inhibitors of CK2 kinase thus demonstrating one of its possible mode of action

Protein kinase CK2 is an antiapoptotic cancer-sustaining protein.

Food Research International 127 (2020) 108730

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/foodres

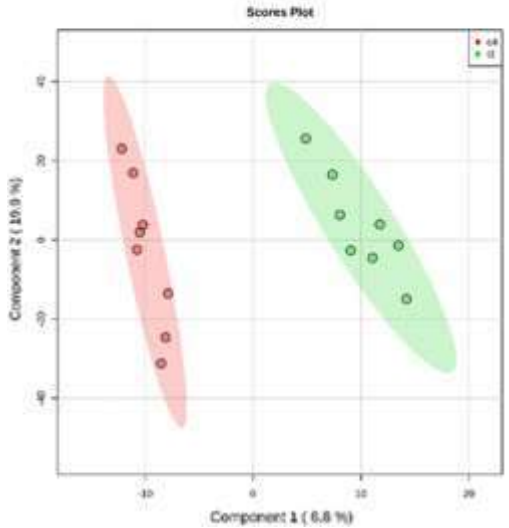
Untargeted UPLC-MS metabolomics reveals multiple changes of urine composition in healthy adult volunteers after consumption of *curcuma longa* L. extract

Gregorio Peron[a,*], Stefania Sut[a], Simone Dal Ben[b], Dario Voinovich[b], Stefano Dall'Acqua[a]

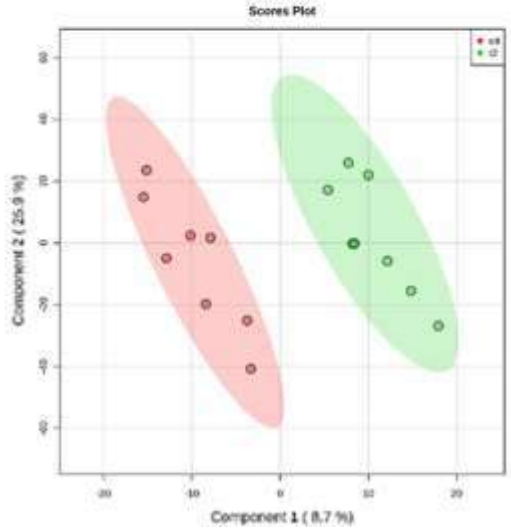
28 days of standardized
Curcuma extract

Metabolomic analysis
Untargeted
Targeted measurements

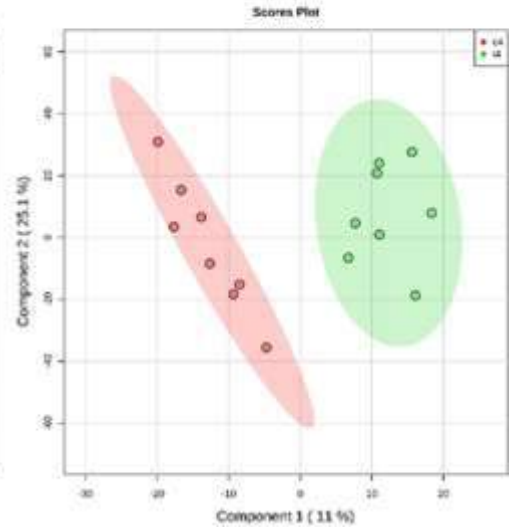
4th control vs. 1st treatment



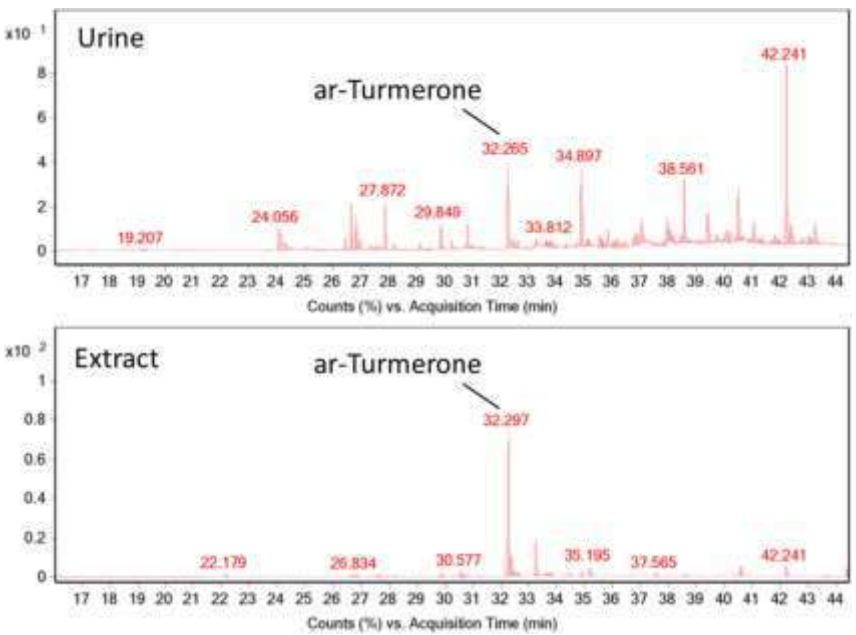
4th control vs. 2nd treatment



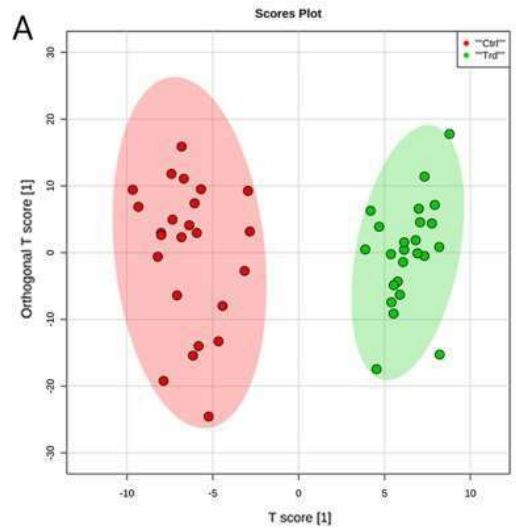
4th control vs. 4th treatment



Changes in urine composition!!



Volatiles constituents of curcuma in urines



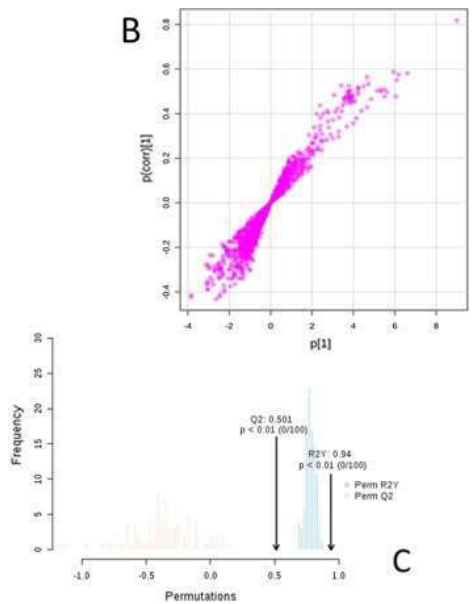
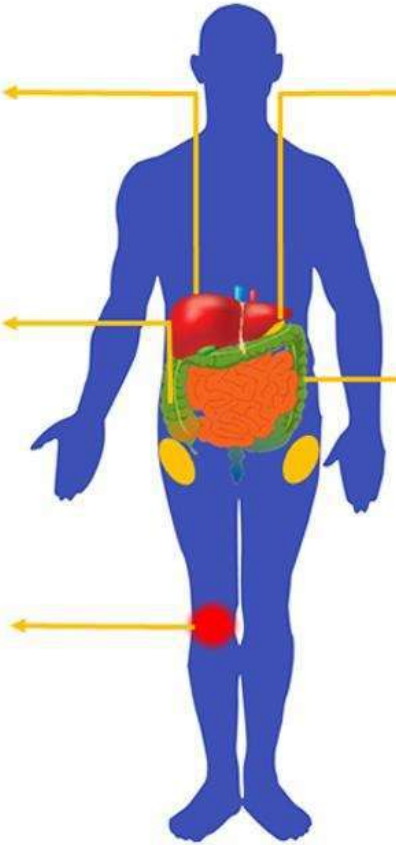


Table 2
Variables positively correlated to supplementation with *C. longa* ($p < 0.05$; p(corr)[1] > 0.4). The features are divided in classes based on the metabolic pathway in which they are involved. Tentative identification (level 2 annotation) was performed searching for accurate *m/z* values in freely available web databases (HMDB and Metlin) and on the basis of the MS^e spectra.

	p(corr)[1]	p[1]	log_2(fold change)	*m/z*	Main fragments (*m/z*)	RT (min)	Tentative ID (*)	METLIN ID
Curcuminoids and metabolites/*C. longa* constituents	0.818	9.49	3.34	357.1689	177.0537, 122.0378	10.9	Hexahydrocurcumin($[M + H\text{-}H_2O]^+$)	71,920
	0.550	6.02	2.54	501.1005	291.0854, 177.0586, 153.0529	11.3	Hesperetin 7-O-glucuronide	96,103
	0.504	3.78	1.34	163.0748	127.532, 91.0567, 77.0400	12.4	4-Hydroxycinnamoylmethane	69,300
	0.497	3.75	1.77	153.0542	65.0372	7.9	Vanillin	62,927
	0.487	4.19	2.09	395.0943	197.0764, 149.0576	8.8	Dihydroferulic acid 4-O-glucuronide**	96,081
	0.485	3.68	1.70	195.0650	145.0277, 117.0351	7.9	Ferulic acid	4156
	0.477	6.44	2.81	409.0963	177.0545, 122.0368	9.7	Dihydrocurcumin($[M + K]^+$)	87,760
	0.457	3.77	2.15	369.1519	177.0535, 145.0285, 117.0348	10.8	Curcumin	44,447
	0.413	4.60	1.75	377.1065	195.0034	10.2	Ferulic acid 4-O-glucuronide($[M + Li]^+$)	96,091
	0.401	4.16	1.95	239.1387	119.0858, 91.0569	11.2	*ar*-Turmerone($[M + Na]^+$)	90,885
Prostaglandines related to inflammation	0.500	5.12	1.32	311.1484	229.1218, 211.1087, 191.0674	10.7	tetranor-PGJM	96,506
	0.479	3.79	1.29	329.1594	275.1256, 229.1221, 211.1089	10.6	tetranor-PGDM	45,422
Metabolism of fatty acids	0.499	4.72	1.77	146.0806	87.0419	3.4	3-Hydroxybutyric acid($[M + ACN + H]^+$)	85,159
	0.483	3.06	1.70	253.1432	213.1465, 167.1461	12.3	Dodecanedioic acid	5596
Activity of gut microbiota	0.473	4.23	1.41	365.1202	183.0643	12.3	Hydroxyphenyllactic acid($[2M + H]^+$)	34,515
	0.469	3.72	1.29	144.1016	98.0993, 68.0468	2.4	Proline-betaine***	7089
Other	0.581	6.72	3.37	230.0484	91.0567	2.6	Benzyl sulfate($[M + ACN + H]^+$)	90,204
	0.497	5.12	2.04	693.3329	339.3236	10.7	PI(22:1(11Z)/0:0)	81,187

*In brackets are indicated the adducts ion, when different to $[M + H]^+$.
**The feature showing p(corr)[1] = 0.448, *m/z* = 390.1392 and RT = 8.8 min was identified as the $[M + NH_4]^+$ adduct of the same metabolite.
***The feature showing p(corr)[1] = 0.574, *m/z* = 287.1965 and RT = 2.2 min was identified as the $[2M + H]^+$ adduct of the same metabolite.

Curcuma metabolomic study: the results



Modification of nicotinic acid metabolism

N1-Methyl-2-pyridone-5-carboxamide
Nicotinuric acid
Trigonelline

Modification of gut microbiota activity

Hydroxyphenylacetylglycine
Phenylacetylglycine
Hydroxyphenyllactic acid
Proline-betaine
Bile acids

Prevention of inflammation

tetranor-PGJM
tetranor-PGDM

Induction of fatty acids metabolism and acylcarnitines turnover

3-Hydroxybutyric acid
Dodecanedioic acid
Acylcarnitines

Intestinal absorption of curcuma constituents and microbial/liver metabolism

Curcumin
Dehydrocurcumin
Hexahydrocurcumin
ar-Turmerone

New informations and approaches

-Study on Healthy human subjects-Multiple metabolic patways are involved: multiple mode of aciton

- -Gut metabolism
- -anti-inflammatory PGD2 pathway
- -fatty acid beta oxidation

-Detection of volatile constituents in urines: possible role of small terpenoids

Food & Function

ROYAL SOCIETY OF CHEMISTRY

REVIEW

Synergic interactions between polyphenols and gut microbiota in mitigating inflammatory bowel diseases

Hao Li, Lindsay M. Chrisman, Ruiqi Li and

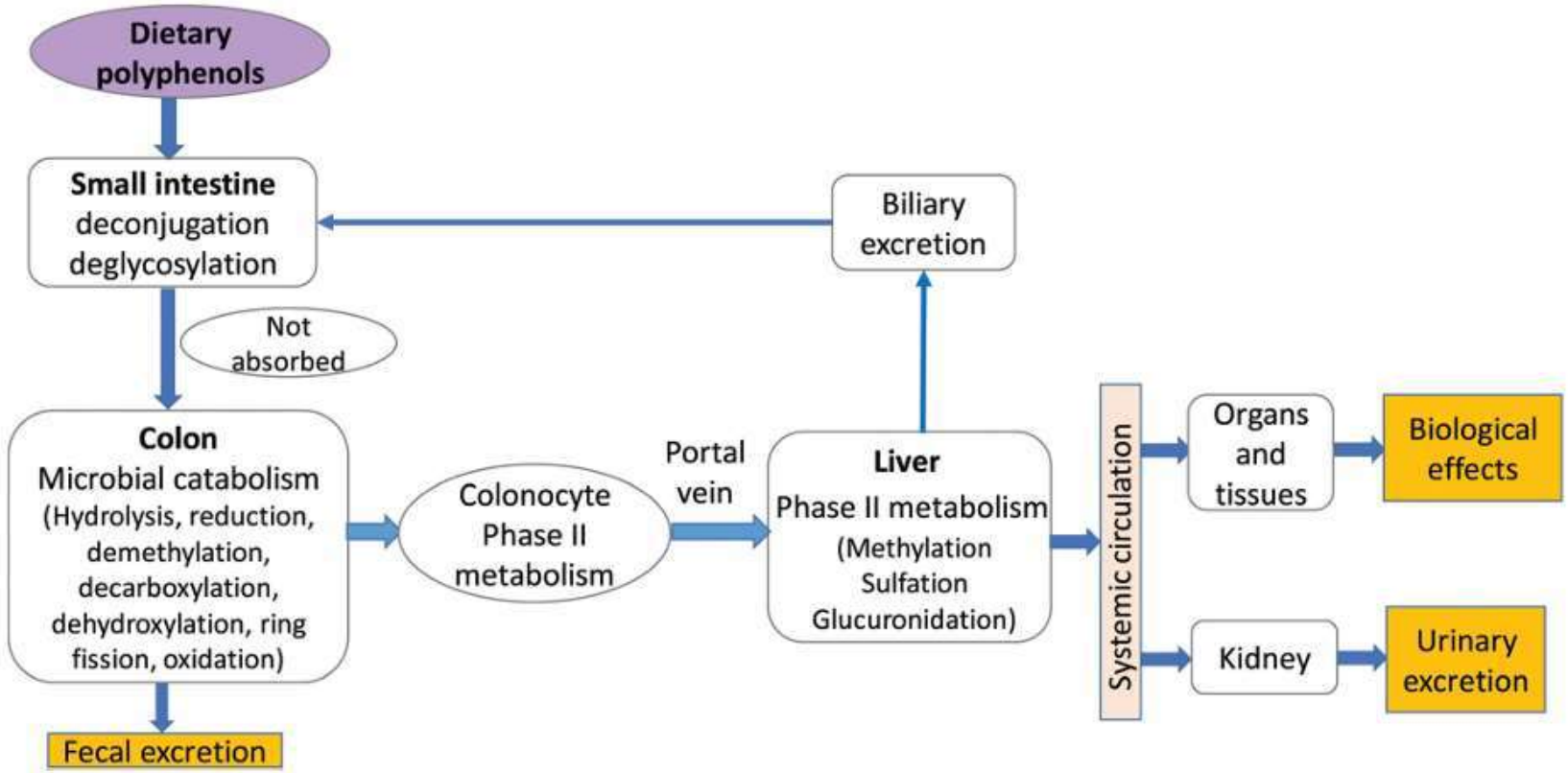


Fig. 1 Microbial catabolism of dietary polyphenols, phase II metabolism and tranport of absorbed microbial metabolites in human. A majority of polyhenols are not absorbed in the small intestine. They are hydrolyzed, demethylated, decarboxylated, dehydroxylated, and ring fissioned by microbiota in colon to produce numerous microbial metabolites. These microbial metabolites undergo phase II metabolism in colon and liver. Part of phase II metabolites re-enter small intestine *via* bibliary excretion. Other metabolites enter systemic circulation to exhibit their biological effects in various organs and tissue. Unabsorbed polyphenols and microbial metabolites are excreted in feces whereas absorbed micrbioal metabolites are mostly excreted in the urine.

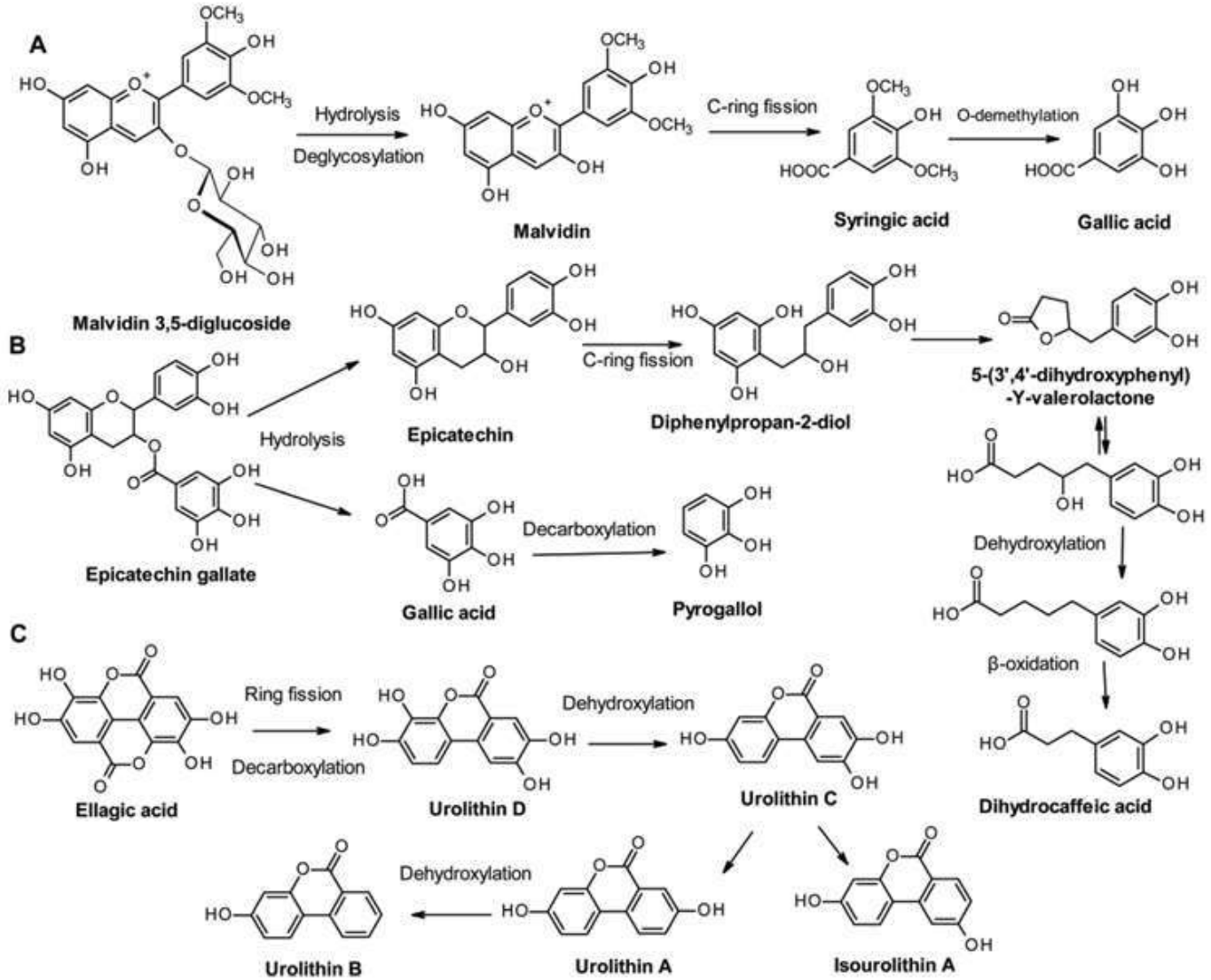
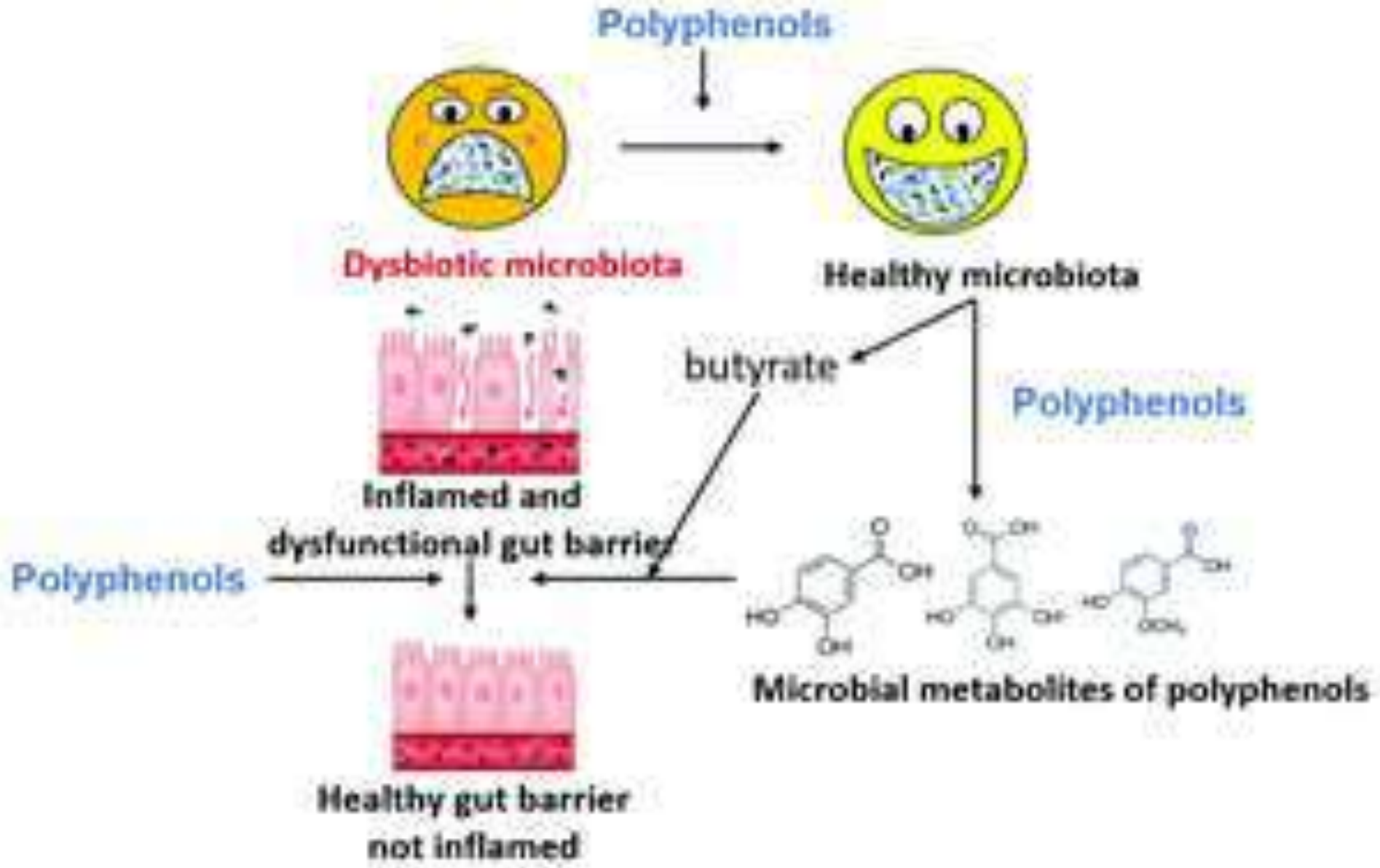
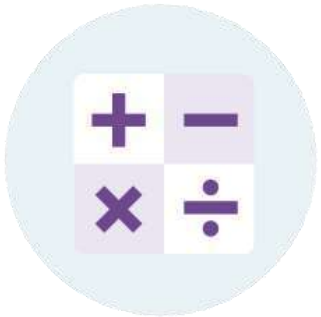


Fig. 2 Microbial catabolism of dietary polyphenols by microbiota in colon using malvidin-3-glucoside, epicatechin gallate, and ellagic acids as examples. (A) Malvidin-3-glucoside is deglycosylated to malvidin. The C-ring fission of malvidin gives rise to syringic acid. Gallic acid is formed after *O*-demethylation of syringic acid. (B) Epicatechin gallate is hydrolyzed to gallic acid and epicatechin. Gallic acid is further decarboxylated to pyrogallol. The C-ring fission of epicatechin yields to diphenylpropan-2-diol which is further degraded to 5-(3',4'-dihydroxyphenyl)-γ-valerolactone. (C) Ring-fission and decarboxylation of ellagic acid yield urolithin D, which loses 1, 2, and 3 hydroxyl groups to form urolinthin C, A, and B, respectively.


Polyphenols
Dysbiotic microbiota
Healthy microbiota
butyrate
Polyphenols
Inflamed and
dysfunctional gut barrier
Polyphenols
Microbial metabolites of polyphenols
Healthy gut barrier
not inflamed

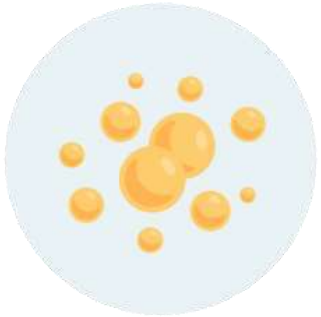
Fattori che influenzano la biodisponibilità di un composto

Processing
(heat, drying)

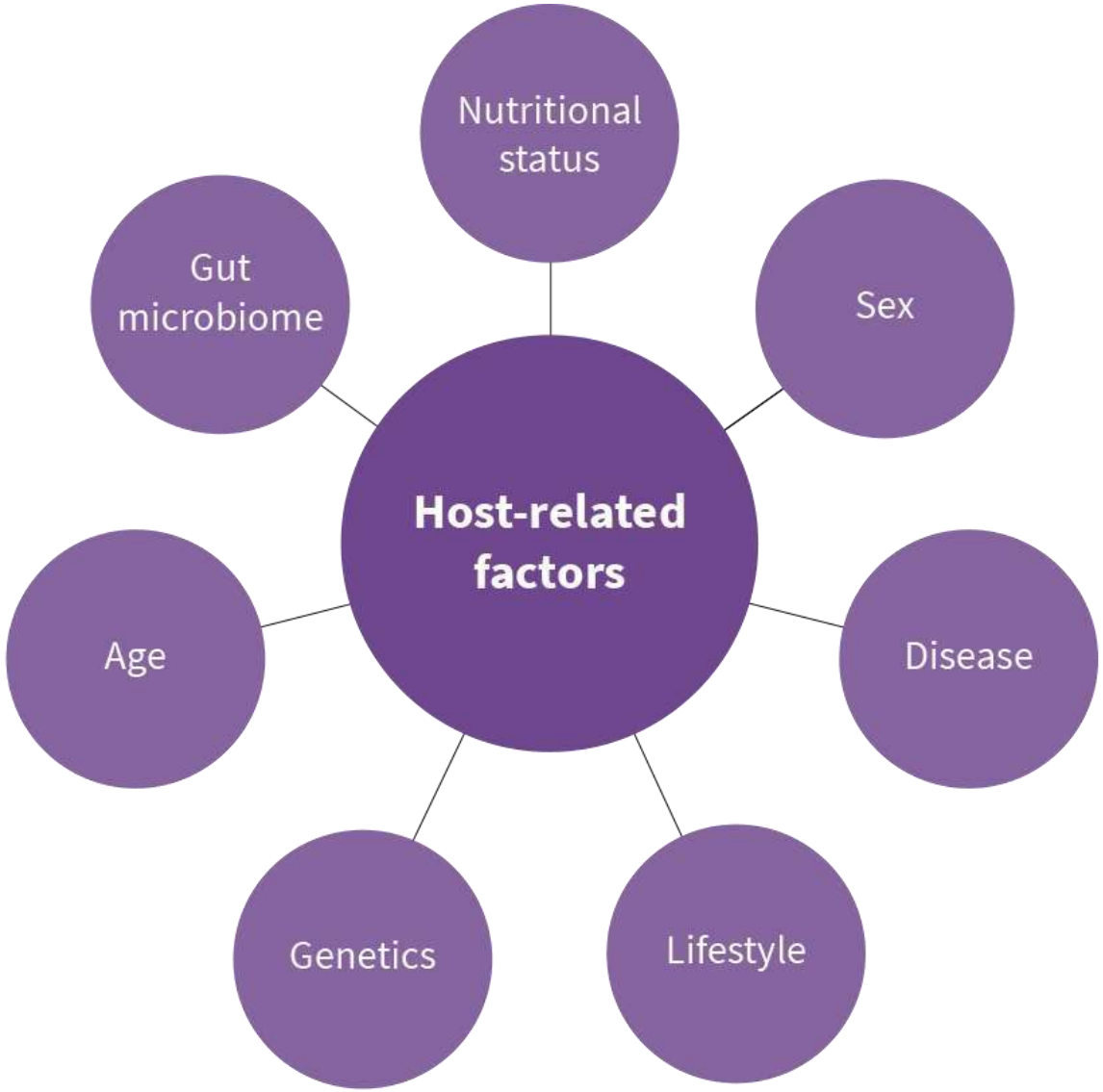


Intake
(dosing, co-ingestion, interactions)

Source
(liquid vs solid, food matrix, encapsulation)



Lipid Presence



Domande?