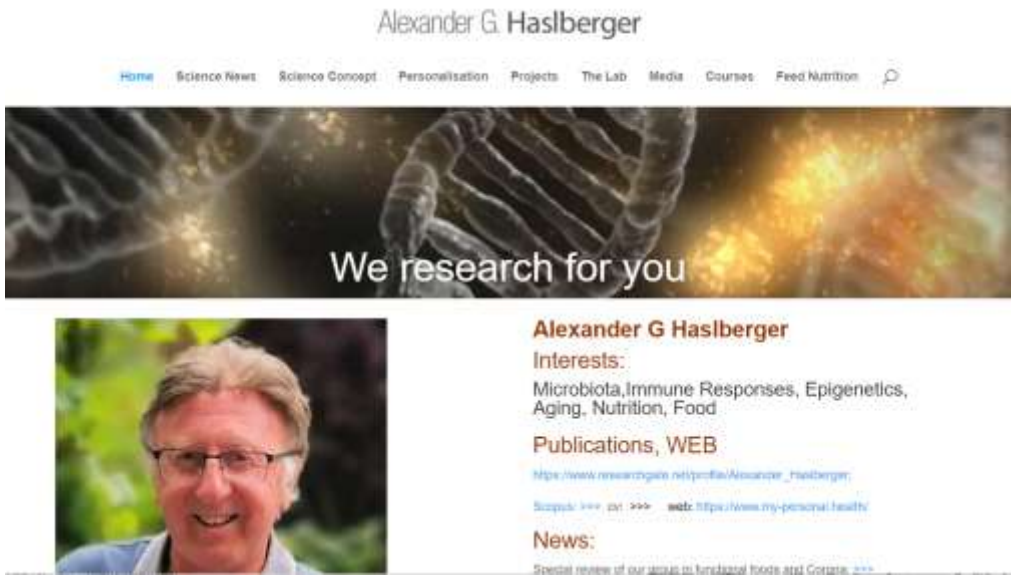
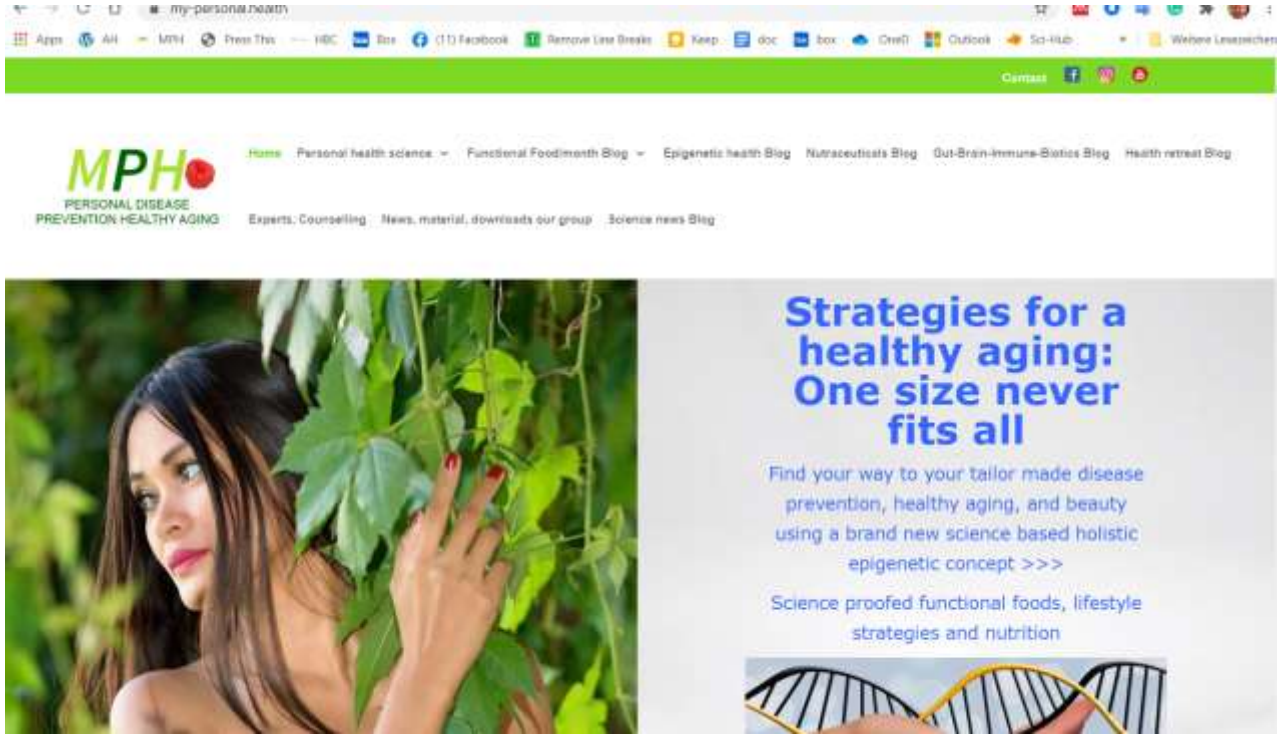
Novel Foods
Haslberger WS 2024

- Development in breeding and biotech
- GVOs, CRISPR
- Cloning and epigenetics
- Foods, microbiota, the I,S. and epigenetics, aging
- Functional foods, pro, pre, syn, post biotics
- Nutraceuticals , medicinal foods
- Fermenting foods, meat
- Foods from new technologies
- Ethnic foods
- Nano in food industry
- Regulations, Health claim, additives, functional food,
- Personalised Nutrition

Materials

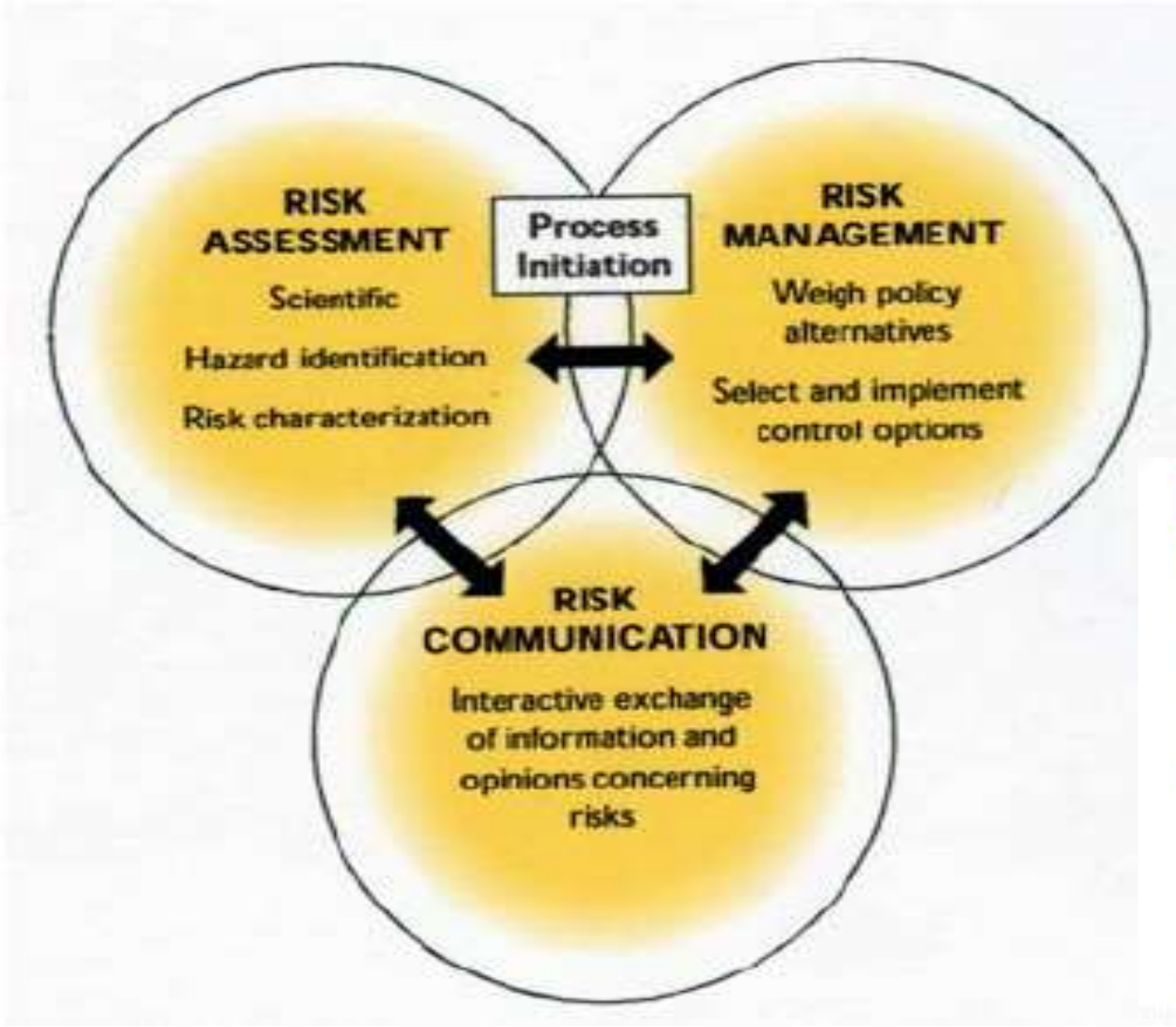

Alexander G. Haslberger
Home
Science News
Science Concept
Personalisation
Projects
The Lab
Media
Courses
Feed Nutrition
We research for you
Alexander G Haslberger
Interests:
Microbiota,Immune Responses, Epigenetics, Aging, Nutrition, Food
Publications, WEB
News:


MPH
PERSONAL DISEASE PREVENTION HEALTHY AGING
Home
Personal health science
Functional Foodmonth Blog
Epigenetic health Blog
Nutraceuticals Blog
Gut-Brain-Immune-Biotics Blog
Health retreat Blog
Experts, Counselling
News, material, downloads our group
Science news Blog
Strategies for a healthy aging: One size never fits all
Find your way to your tailor made disease prevention, healthy aging, and beauty using a brand new science based holistic epigenetic concept >>>
Science proofed functional foods, lifestyle strategies and nutrition

Functional ingredients – from fiction to facts

Food habits have greatly evolved in recent decades. In addition to aspects such as taste, quality, safety, and convenience, consumers now also expect processed food to be nutritious and sustainable. Factors such as our ageing population; growing levels of obesity and type II diabetes; and increased occurrence of cardiovascular diseases have urged consumers to seek, beyond nutritional requirements, health-promoting benefits in the food they consume. Interest in these so-called functional foods has thus drastically increased in recent years.

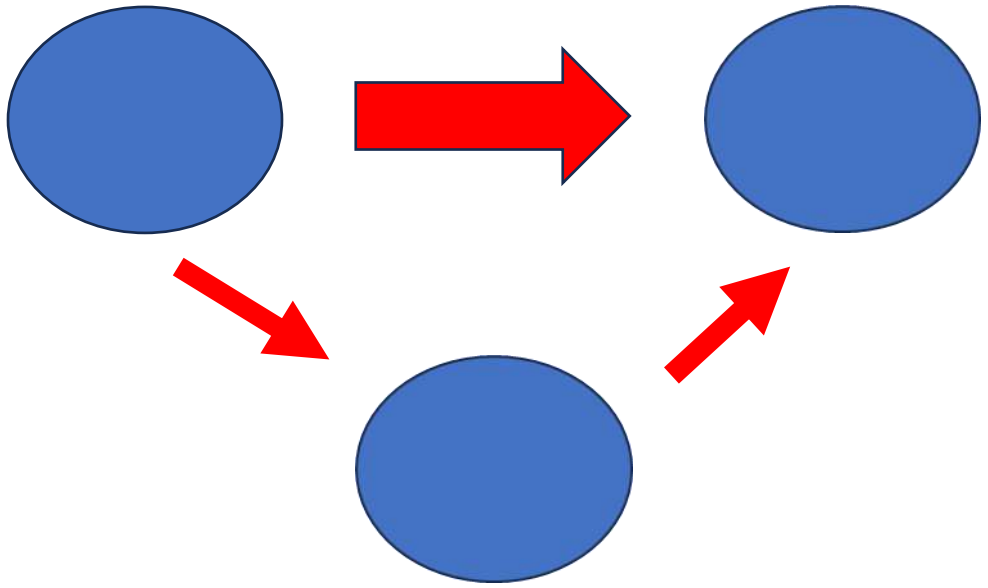
WHO , UN, Risk Assessment

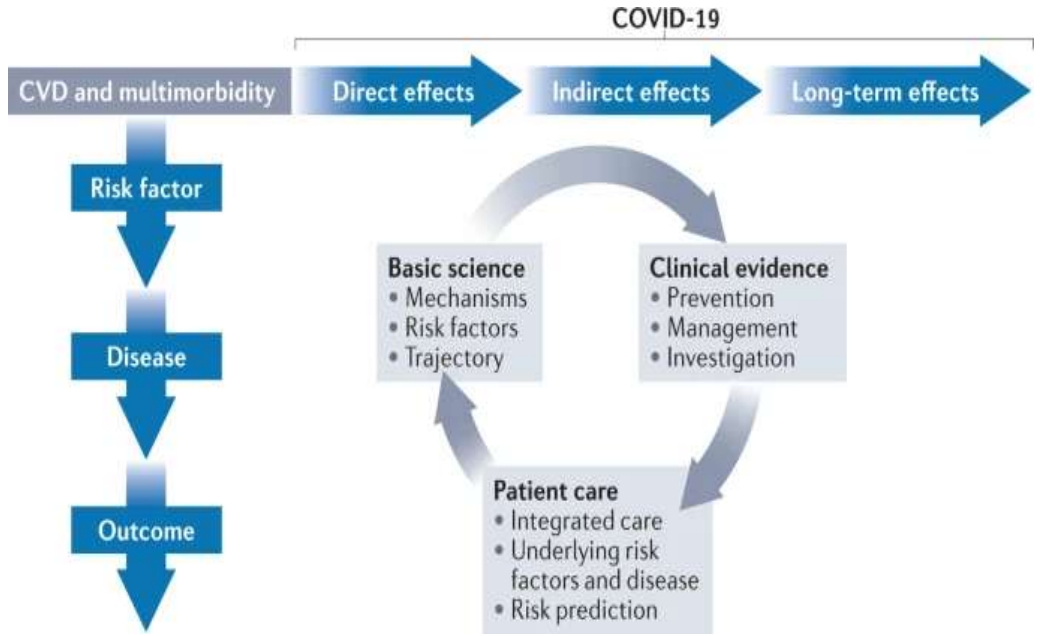


Examples for risk and uncertainty:

Particular	Risk	Uncertainty
Knowledge	Perfect knowledge	Imperfect knowledge
Outcome	Known	Not known
Probability	Known	Not known
Measurement	Measurable	Not measurable
Insurance	Insurable	Not insurable
Example	→Incidence of pest and diseases (negative) → Shortfall in rainfall (negative) → Fixed capital investments (positive) →Monsoon failure / drought (negative)	→Implications of Chinese Corona Virus (COVID-19) pandemic →Outbreak of Avian flu → Technology uncertainty

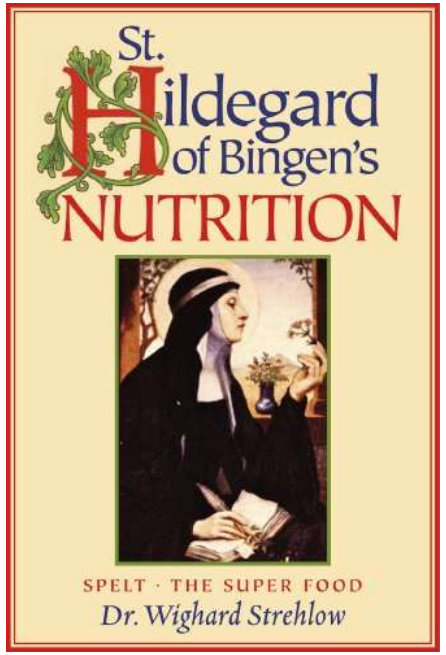
Direct, indirect risk, (long term) Epidemiologie





Nutrition, Foods , Health

Nutrition is the biochemical and physiological process by which an organism uses food to support its life.	Hippocrates, “**Let food be thy medicine, and let medicine be thy food**”



Foods, functions, claims

Biotechnology and Agriculture, development

Plant Selection

・Agriculture begins with the collection and planting of seeds from wild plants

・Occurs in 8 locations throughout the world between 7000 -12000 years ago

・Selections were made based on yield, seed size, and taste

Landraces, Diversity

Refers to the particular kinds of old seed strains and varieties that are farmer-selected in areas where local subsistence agriculture has long prevailed. Landraces are highly adapted to specific locales or groups.

Definition :
modified by native and also immigrant farmers.

The term is usually applied to varieties of corn, squash, and beans that were domesticated by native farmers,

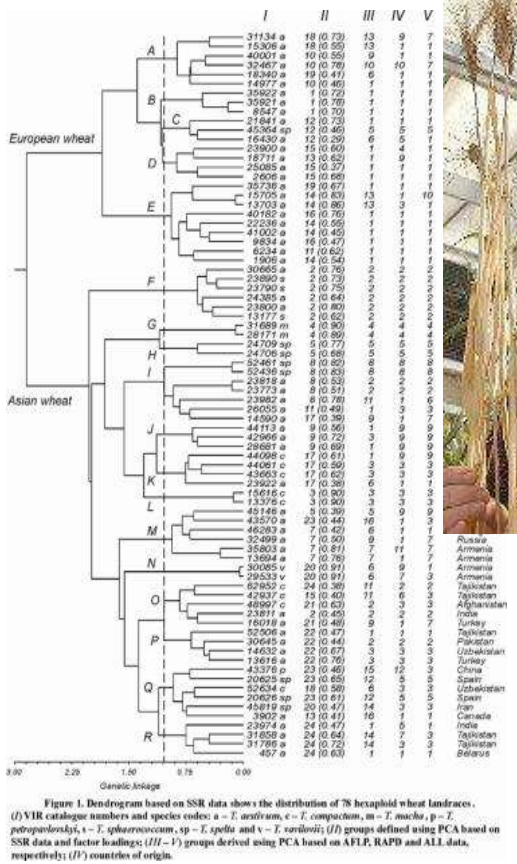
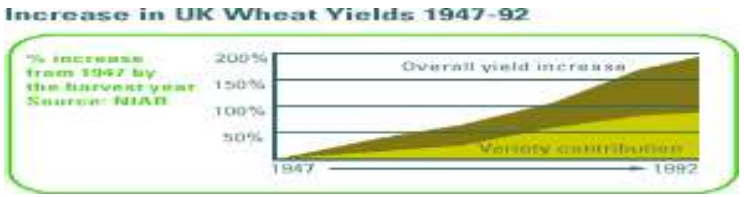


Figure 1. Dendrogram based on SSR data shows the distribution of 78 hexaploid wheat landraces. (*I*) VIR catalogue numbers and species codes: a – *T. aestivum*, c – *T. compactum*, m – *T. macha*, p – *T. petropavlovskyi*, s – *T. sphaerococcum*, sp – *T. spelta* and v – *T. vavilovii*; (*II*) groups defined using PCA based on SSR data and factor loadings; (*III* – *V*) groups derived using PCA based on AFLP, RAPD and ALL data, respectively; (*IV*) countries of origin.

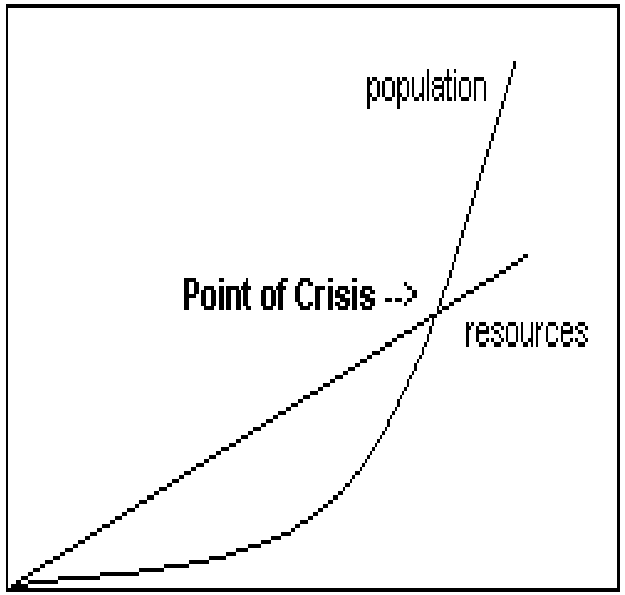
GREEN Revolution

Term coined by U.S. Agency 1968)
Movement to increase yields by using:
. New crop cultivars
. Irrigation
. Fertilizers
. Pesticides
. Mechanization

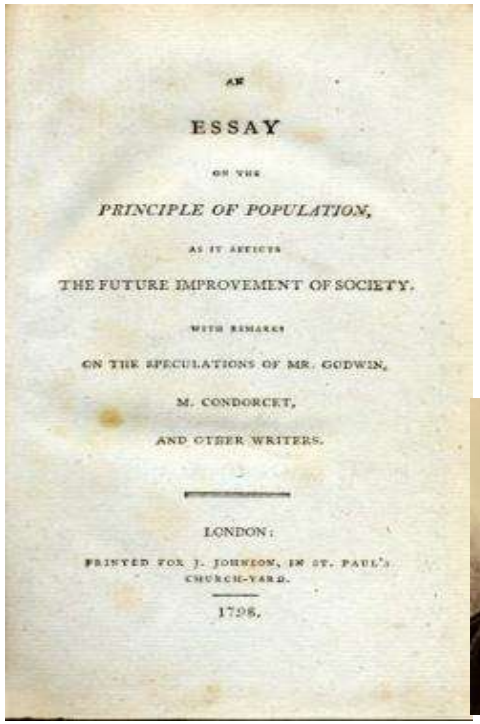


A planned international effort funded by: Rockefeller Foundation
Ford Foundation
Many developing country governments
Purposed to eliminated hunger by improving crop performance Norman Borlaug (1970 Nobel price)

T. Malthus: 1766- 1834
Crisis in food production



Malthus' Basic Theory


AN

ESSAY

ON THE

PRINCIPLE OF POPULATION,

AS IT AFFECTS

THE FUTURE IMPROVEMENT OF SOCIETY.

WITH REMARKS

ON THE SPECULATIONS OF MR. GODWIN,

M. CONDORCET,

AND OTHER WRITERS.

LONDON:

PRINTED FOR J. JOHNSON, IN ST. PAUL'S CHURCH-YARD.

1798.

Models for population growth and food security:

Pessimistic or Alarmist Theory

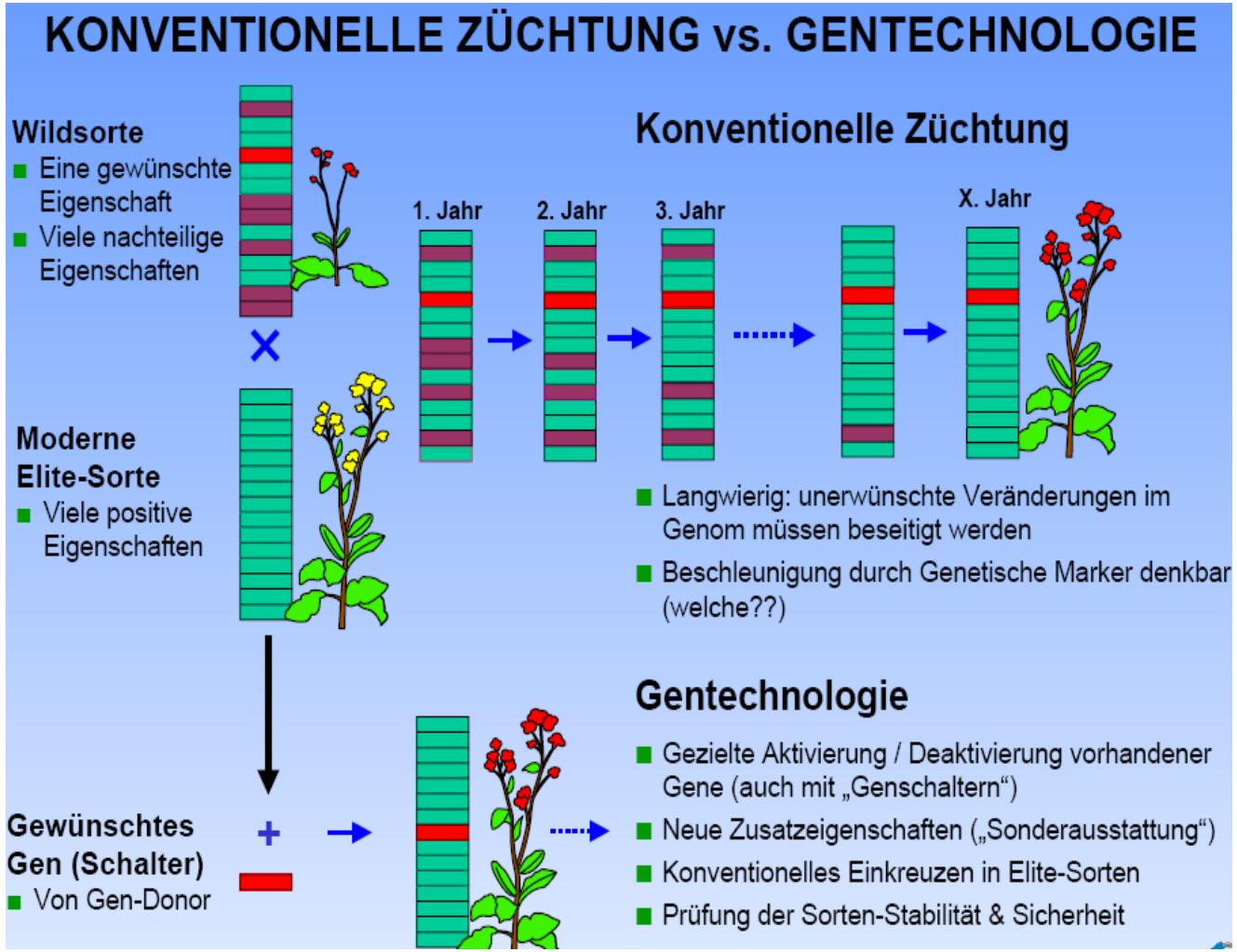
Malthus - 19th century, Coale & Hoover (1958),
Paul Ehrlich (Population Bomb),
Meadows (Limits to Growth) – 1960s and 1970s.
Focus on population policy & fixed, non-renewable resources.

Optimistic Theory
Ester Boserup – 1960s – 70s (agric. Intensification)
Julian Simon – 1970s - 80s (human capital)

Neutralist or Revisionist Theory

Pflanzenzüchtung

Breeding, yield, time for development



Klassische Züchtungsmethoden

Auslesezüchtung/Selektionszüchtung
Die Auslesezüchtung fängt mit dem Anbau von Genotypengemischen (vorh. genetische Linien, auch Wildpflanzen) an. Aus dem nach gemeinsamer Abblüte erzeugten Saatgut werden Pflanzen mit vorteilhaften Eigenschaften ausgewählt (Zuchtwahl, Massenauslese).
Kombinationszüchtung
Die Kombinationszüchtung ist eine Kreuzung verschiedener Genotypen (Linien). Es entsteht ein neuer Genotyp

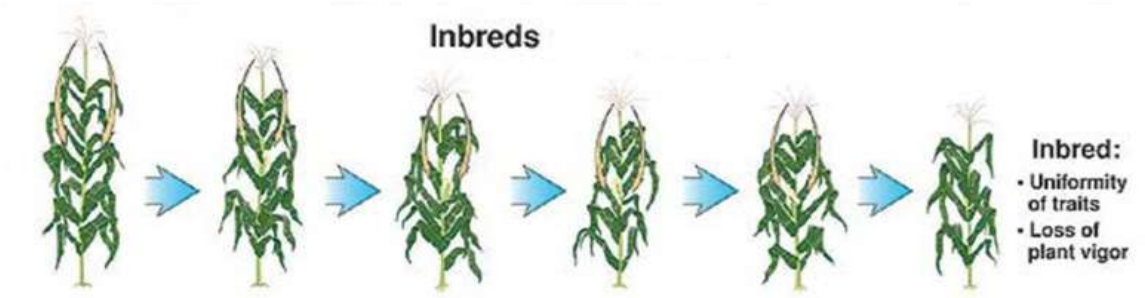
Heterosiszüchtung
In der Heterosiszüchtung werden bei Fremdbefruchtern (Mais, Roggen…) in mehrjähriger Züchtung aus heterozygoten Ausgangspflanzen nahezu homozygote Inzuchtlinien gezüchtet. Kreuzt man zwei solche Linien, tritt bei der F1 Generation oft eine auffallende Mehrleistung gegenüber der Elternformen auf. Dies nennt man „Heterosis-Effekt

Hybridzüchtung
Die Hybridzüchtung ist ein Beispiel für Heterosiszüchtung, zur Erzielung einer hohen markt- oder betriebsgerechten pflanzlichen Produktion durch Bastardwüchsigkeit. So werden bei der Hybridzüchtung geeignete, gesondert gezüchtete Inzuchtlinien einmalig miteinander gekreuzt (Einfachhybride). [1] Die Nachkommen der ersten Generation (F1) einer solchen Kreuzung haben gegenüber der Elterngeneration ein üppigeres Wachstum (Heterosiseffekt
Für den Landwirt bedeutet dies jedoch, dass das Saatgut jedes Jahr wieder neu bezogen werden muss, wenn er den Ertragsvorteil gegenüber Nicht-Hybriden weiterhin erhalten will, da der Heterosiseffekt nur in der F1-Generation auftritt und danach wieder verloren geht.

Mutationszüchtung
Bei der Mutationszüchtung werden Samen Röntgen- oder Neutronenstrahlen, Kälte- und Wärmeschocks oder anderen Mutagenen ausgesetzt[2], um neue Eigenschaften durch Mutation zu erzielen, die einen positiven Effekt aufweisen. Damit wird die Züchtung neuer Sorten erheblich beschleunigt.

Hybridzüchtung, Heterosis

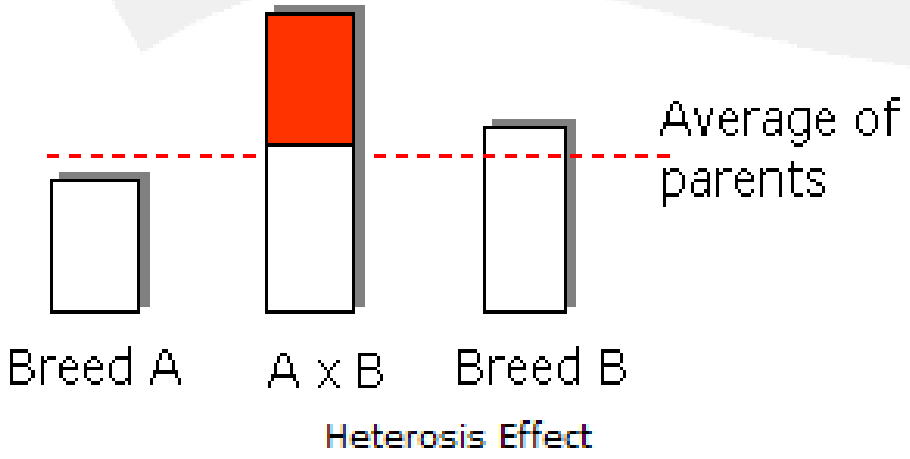
- Three Main Principles
  - Inbreeding
  - Hybridization
  - Heterosis
    - Main Goals
      - Increase the homozygosity at all or specific loci in the plant genome
      - Produce a plant which breeds true
      - Produce uniform plants



Hybrid: Heterosis effect

The purpose of crossing is to make use of the heterosis effect partly to improve fertility and partly to combine the different characteristics for which the lines were previously selected. For meat production a desirable quality in the final product is to produce large numbers of rapidly growing individuals. This requires good fertility in the mother combined with good growth rate in the progeny.

The heterosis effect makes the hybrid pigs better than the average of the parents. The traits with the lower heritability show the largest heterosis effect. This is particularly true for fertility, mothering abilities and body structure, which have a low heritability.



Heterosis Effect

Introducing new traits in a plant family:(Random) Mutation Breeding

Examples of plants that were produced via mutation breeding are given in the table below.

Crop	Cultivar Name	Method Used to Induce Mutation
rice	Calrose 76	gamma rays
wheat	Above	sodium azide
	Lewis	thermal neutrons
oats	Alamo-X	X-rays
grapefruit	Rio Red	thermal neutrons
	Star Ruby	thermal neutrons
burmuda grass	Tifeagle	gamma rays
	Tifgreen II	gamma rays
	Tift 94	gamma rays
	Tifway II	gamma rays
lettuce	Ice Cube	ethyl methanesulphonate
	Mini-Green	ethyl methanesulphonate
common bean	Seafarer	X-rays
	Seaway	X-rays
lilac	Prairie Petite	thermal neutrons
St. Augustine grass	TXSA 8202	gamma rays
	TXSA 8212	gamma rays

Quite a few flower cultivars have been developed via mutation breeding, among them some of the cultivars of *Alstroemeria*, begonia, carnation, chrysanthemum, dahlia, and snapdragon.

IAEA

Why Radiation Induced Mutation?

Pierre Lagoda, Head of the FAO/IAEA Plant Breeding and Genetics Section, explains why 'induced mutation breeding' is a practical, sustainable solution to the world's food crisis.

"We offer a very efficient tool to the global agricultural community to broaden the adaptability of crops in the face of climate change, rising prices, and soils that lack fertility or have other major problems," says Lagoda.

Induced mutation: half the time of traditional breeding methods. Routinely, plant breeding requires seven to 10 years of research to produce a promising new variety. A breeder looking for pest resistance, for example, might find the characteristic in a wild variety with poor quality and yield. This wild variety will be crossed with a plant that does have good quality and yield, and any offspring combining the desired traits will then be selected and propagated.

Induced mutation: more options from which breeders can choose. Hybrids, the product of crosses, are only as resilient and productive as the source parents. Over the past century, about 75% of crop biodiversity has been lost and monoculture has diminished plant variety in farmers' fields.

Both conditions limit researchers when crossing strains to create new plants. "This loss in plant genetic diversity endangers food security as resistance to yet latent biotypes of pests and diseases and extreme weather conditions may have become severely weakened," says Lagoda.

There is a solution: using radiation to artificially induce the variations that plant breeders need. Radiation-induced mutation produces millions of variants. Breeders then screen for the desired traits and crossbreed. "Induced mutation breeding is a safe and proven technology. The method does encounter resistance and the public is generally concerned by anything relating to radiation and mutation," Lagoda explains.

"In plant breeding we're not producing anything that's not produced by nature itself. There is no residual radiation left in a plant after mutation induction. Through its Technical Cooperation Programme, the IAEA provides the tool and the expertise, then national agricultural research systems and plant breeders must take the next step; selecting and cross-breeding plants to achieve the desired result," says Lagoda.

Pierre Lagoda, Head of the FAO/IAEA Plant Breeding and Genetics Section. E-mail: P.J.L.Lagoda@iaea.org

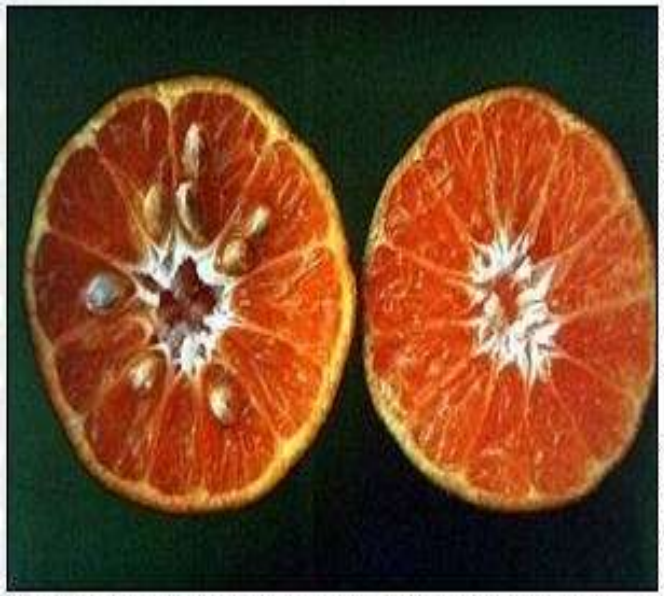
Breeding: Irradiation

Breeding: Irradiation

Irradiator at Institute of Radiation Breeding
Ibaraki-ken, JAPAN
(http://www.irb.affrc.go.jp/)

Mutation breeding

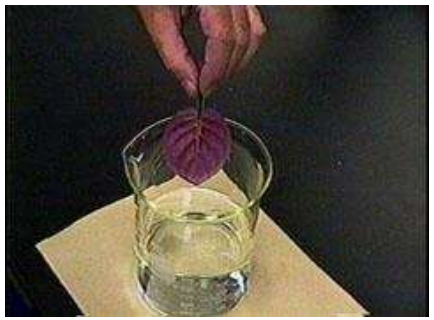
Since the start of the citrus breeding programme five cultivars have been released from the conventional breeding programme. Currently final market evaluation of selected hybrids A25, B17, B24 and Q38 is underway to determine if they can be commercialised. Hybrids I22, B17 and B24 are in the process of semi-commercial evaluation.

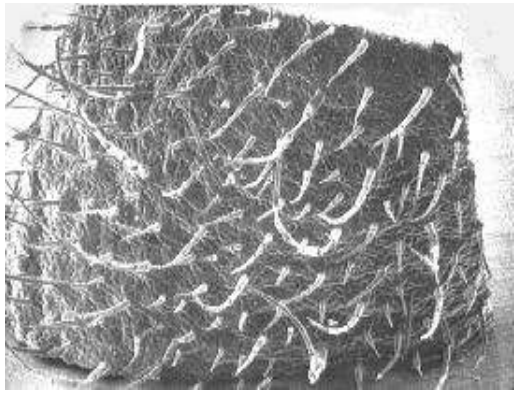


Mutation breeding is currently conducted as a supplement to the conventional breeding programme. It is an economical and time saving method to alter a single characteristic (e.g. seediness) of a cultivar, without changing the rest of its genetic composition. Conventional breeding, followed by mutation breeding, can provide a means of producing new seedless cultivars with a wider range of colour, quality and time of maturity.

Sakkie Froneman reported on the ARC-ITSC's successes with citrus mutation breeding in the January 1999 issue of the Institute's quarterly magazine, *Neltropika*. Contact Mrs Iris Human at E-mail: iris@itsc.agric.za to order a copy of the article.

Tissue culture , Clones ?



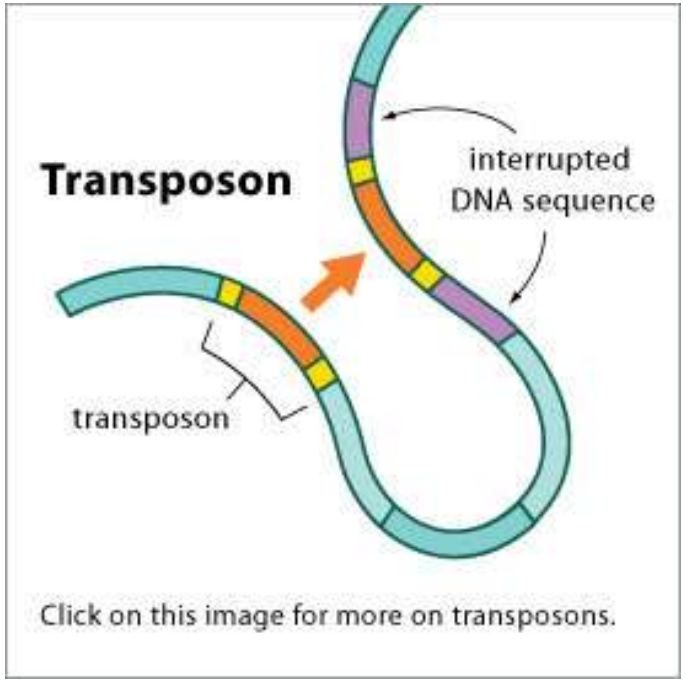


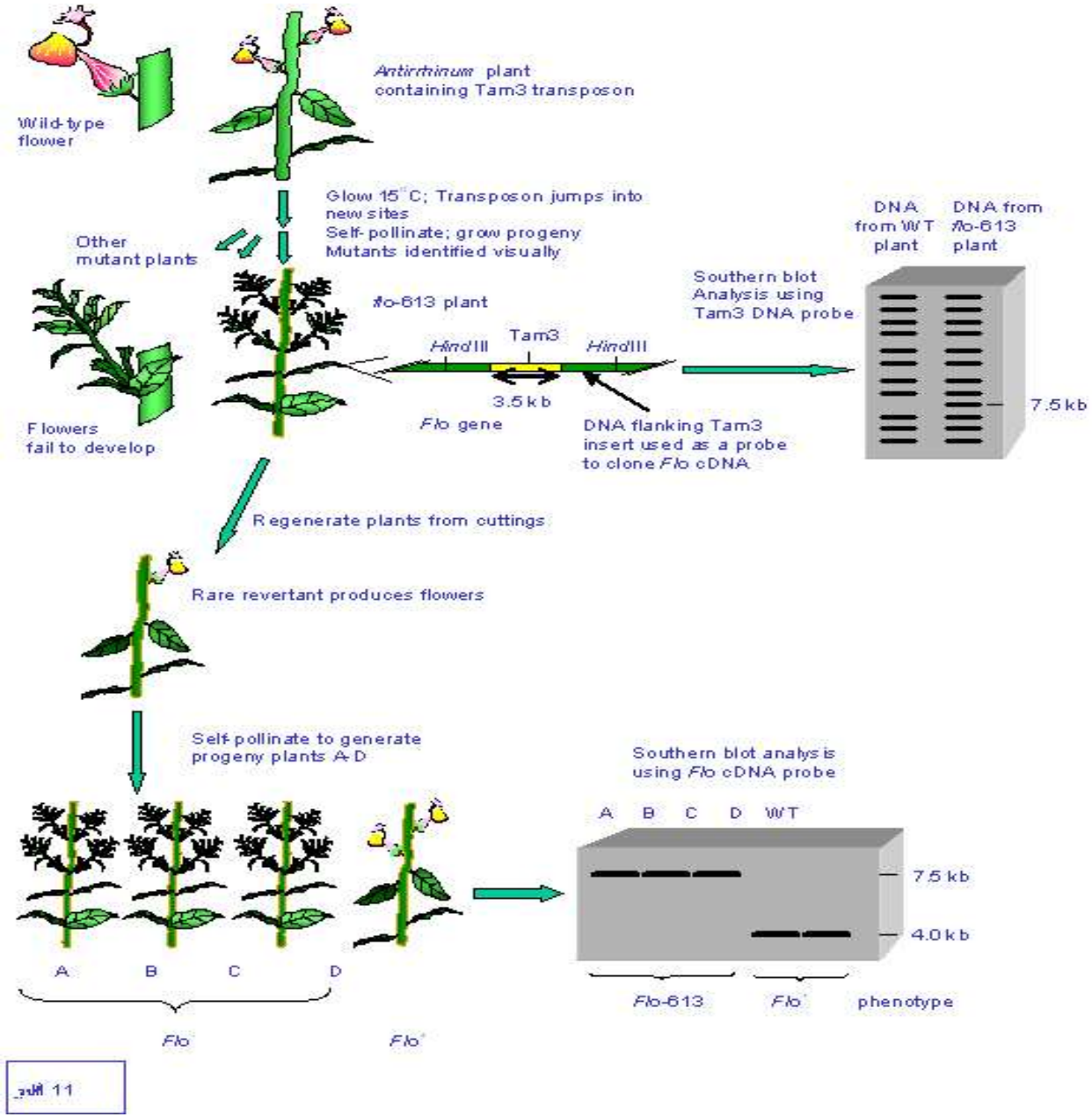
Somaclonal variation

- Production of a new variety of japanese butterbur using somaclonal variation.(upper:new variety, lower:native variety)

Breeding using transposons

Ein Transposon ist ein DNA-Abschnitt bestimmter Länge im Genom, der seine Position im Genom verändern kann (Transposition). Man unterscheidet Transposons, deren mobile Zwischenstufe von RNA gebildet wird (Retroelemente oder Klasse-I-Transposon), von denjenigen, deren mobile Phase DNA ist (DNA-Transposon oder Klasse-II-Transposon).





Transposon tagging

The molecular isolation of transposable elements now permits the cloning of genes in which the element resides. The major advantage of this system is that genes whose function is not known can be cloned

Molecular marker directed breeding

Welcome to Innovative Methods for Rice Breeding - Combining Participatory Plant Breeding (PPB) with Molecular Marker Techniques

This photo shows women farmers in Orissa (Eastern India) making selections from bulks that we made using marker-assisted selection for root length and aroma. You can still see variation for plant height and flowering time in the bulk population. These farmers selected the early plants with long and thick straw.

The project is funded by the Plant Sciences Programme of DFID, managed by the Centre for Arid Zone Studies, University of Wales, Bangor.

Through this website we aim to provide a useful and interesting resource for all those interested in improving rice breeding methods.

Cloning, Definition

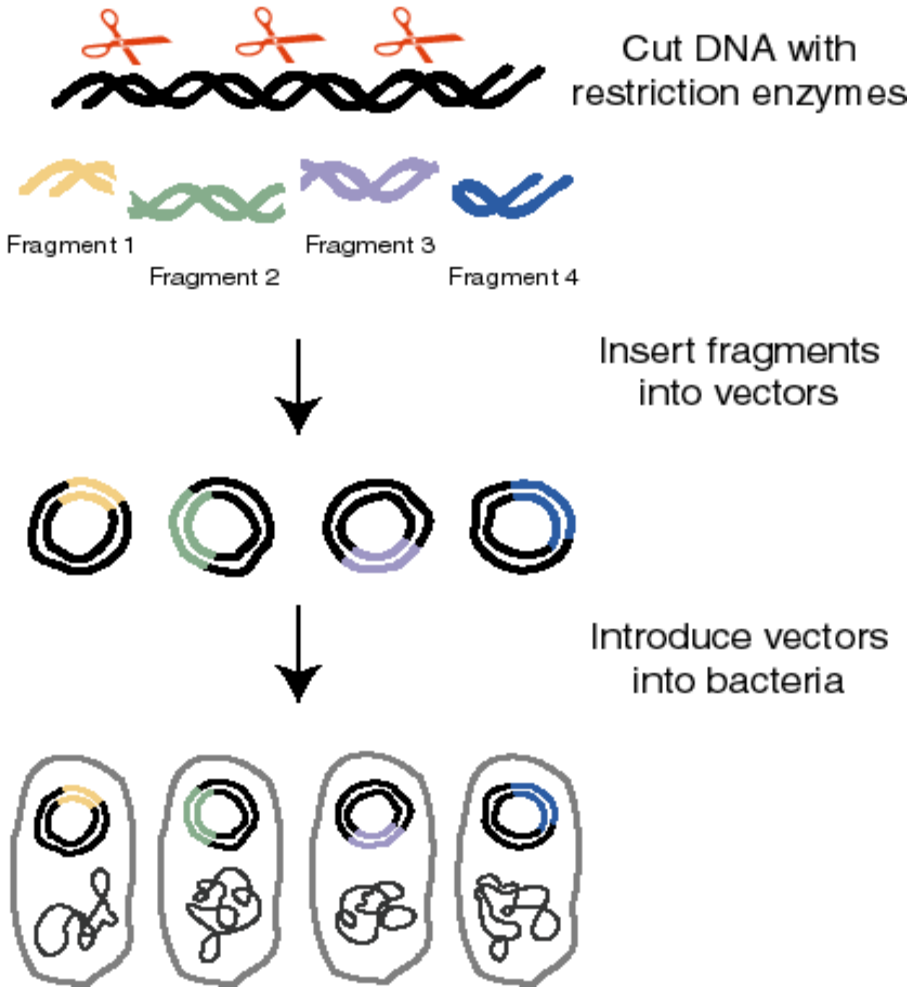
Cloning is the process of making an identical copy of something

In biology, it collectively refers to processes used to

-- copies of DNA Fragments (molecular cloning)
-- cells (cell cloning)
-- organism

The term also covers when organisms such as bacteria, insects or plants reproduce asexually.

DNA cloning:

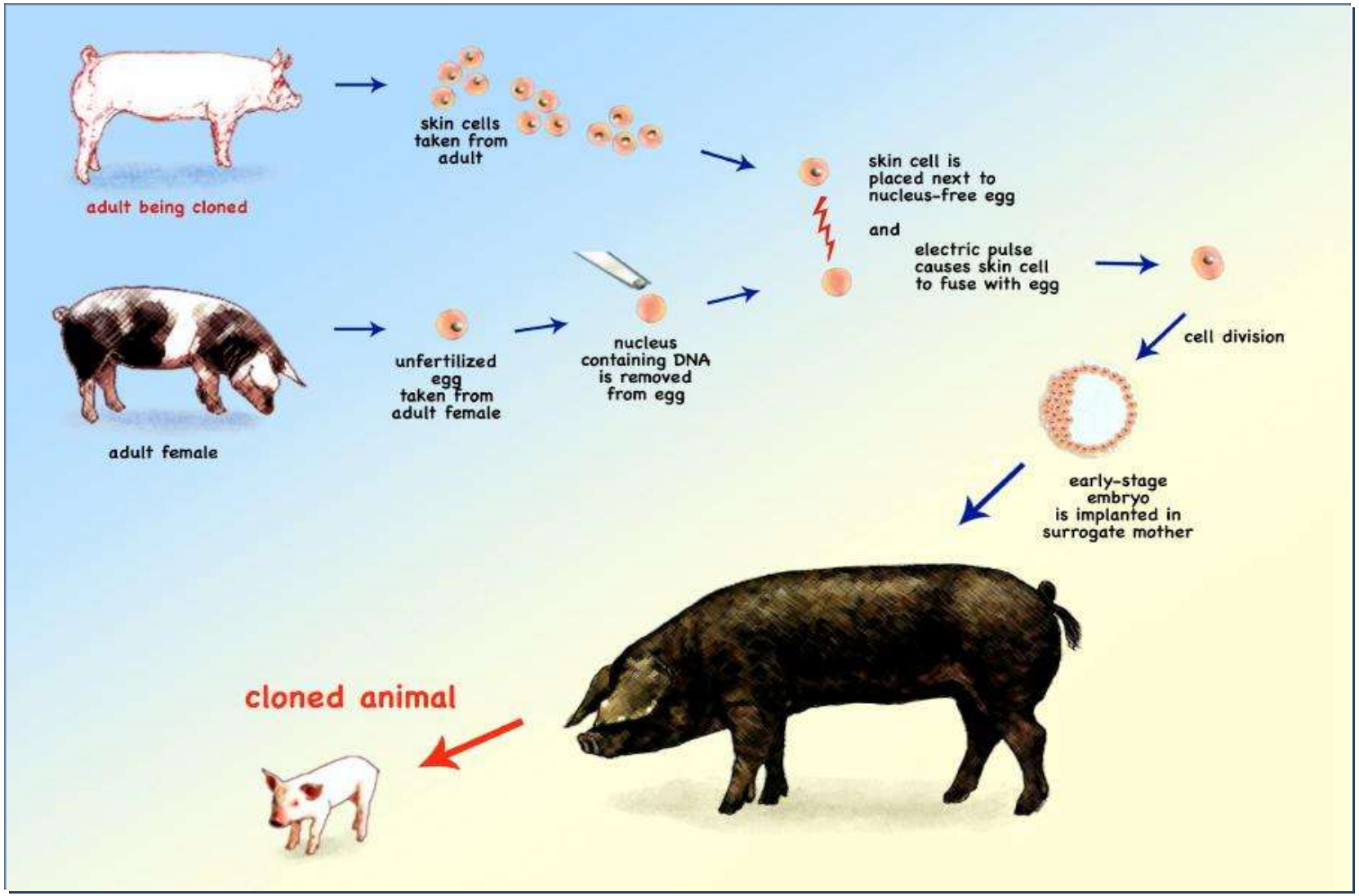


To clone a piece of DNA, DNA is cut into fragments using restriction enzymes that recognize specific sequences of bases in DNA. The fragments are pasted into vectors that have been cut by the same restriction enzyme. Vectors (e.g., plasmids or viruses) are needed to transfer and maintain DNA in a host cell.

Reproductive Cloning

Reproductive cloning is a technology used to generate an animal that has the same nuclear DNA as another currently or previously existing animal. Dolly was created by reproductive cloning technology. In a process called "somatic cell nuclear transfer" (**SCNT**), scientists transfer genetic material from the nucleus of a donor adult cell to an egg whose nucleus has been removed. The reconstructed egg containing the DNA from a donor cell must be treated with chemicals or electric current in order to stimulate cell division. Once the cloned embryo reaches a suitable stage, it is transferred to the uterus of a female host where it continues to develop until birth.

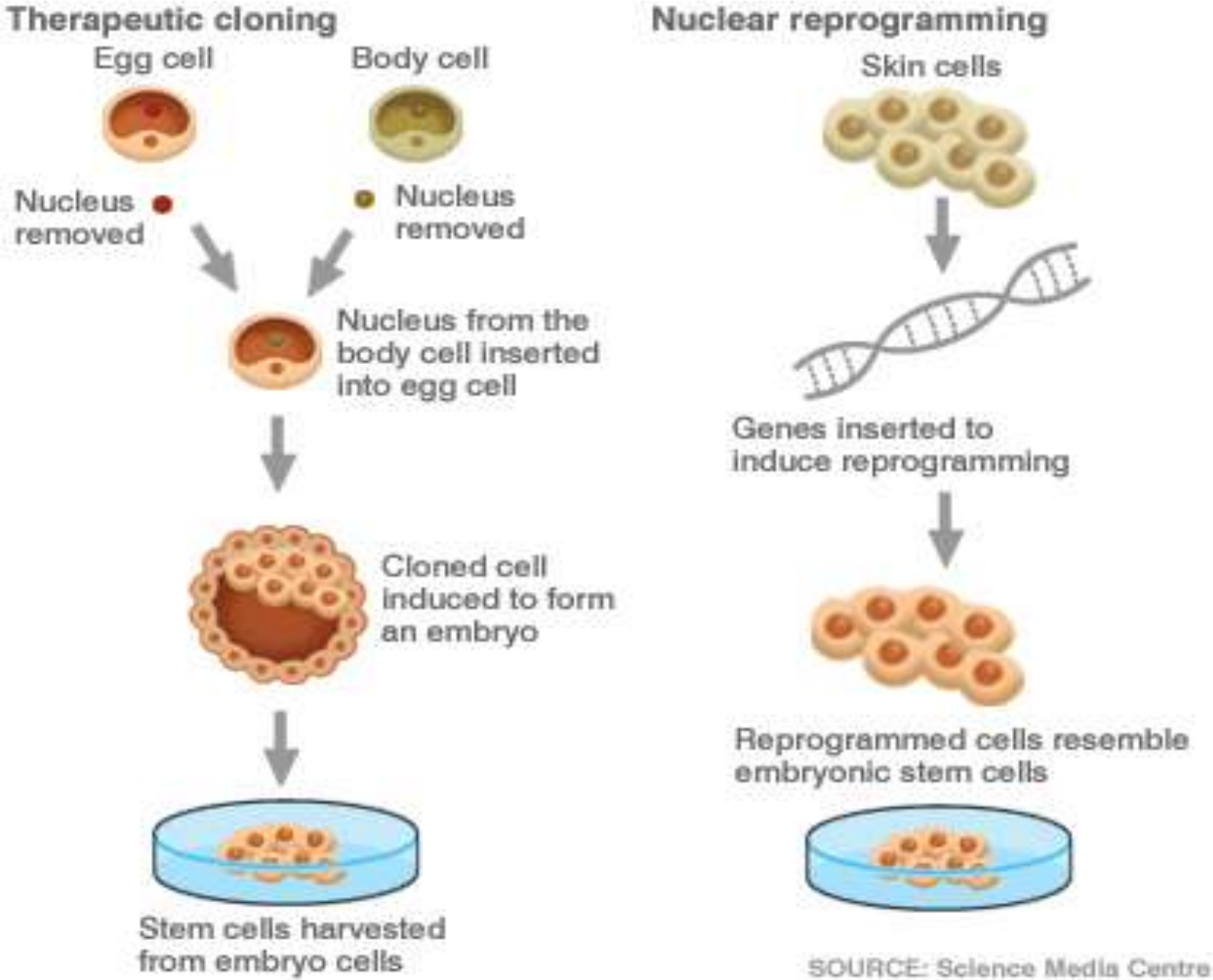
Reproductive Cloning



Therapeutic Cloning

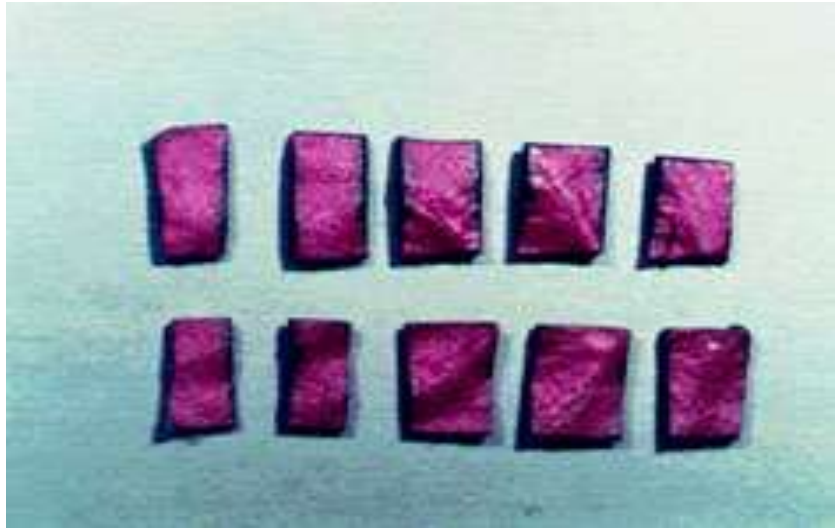
Therapeutic cloning, also called "embryo cloning," is the production of human embryos for use in research. The goal of this process is not to create cloned human beings, but rather to harvest stem cells that can be used to study human development and to treat disease. Stem cells are extracted from the egg after it has divided for 5 days.

The extraction process destroys the embryo, which raises a variety of ethical concerns. Many researchers hope that one day stem cells can be used to serve as replacement cells to treat heart disease, Alzheimer's, cancer, and other diseases.

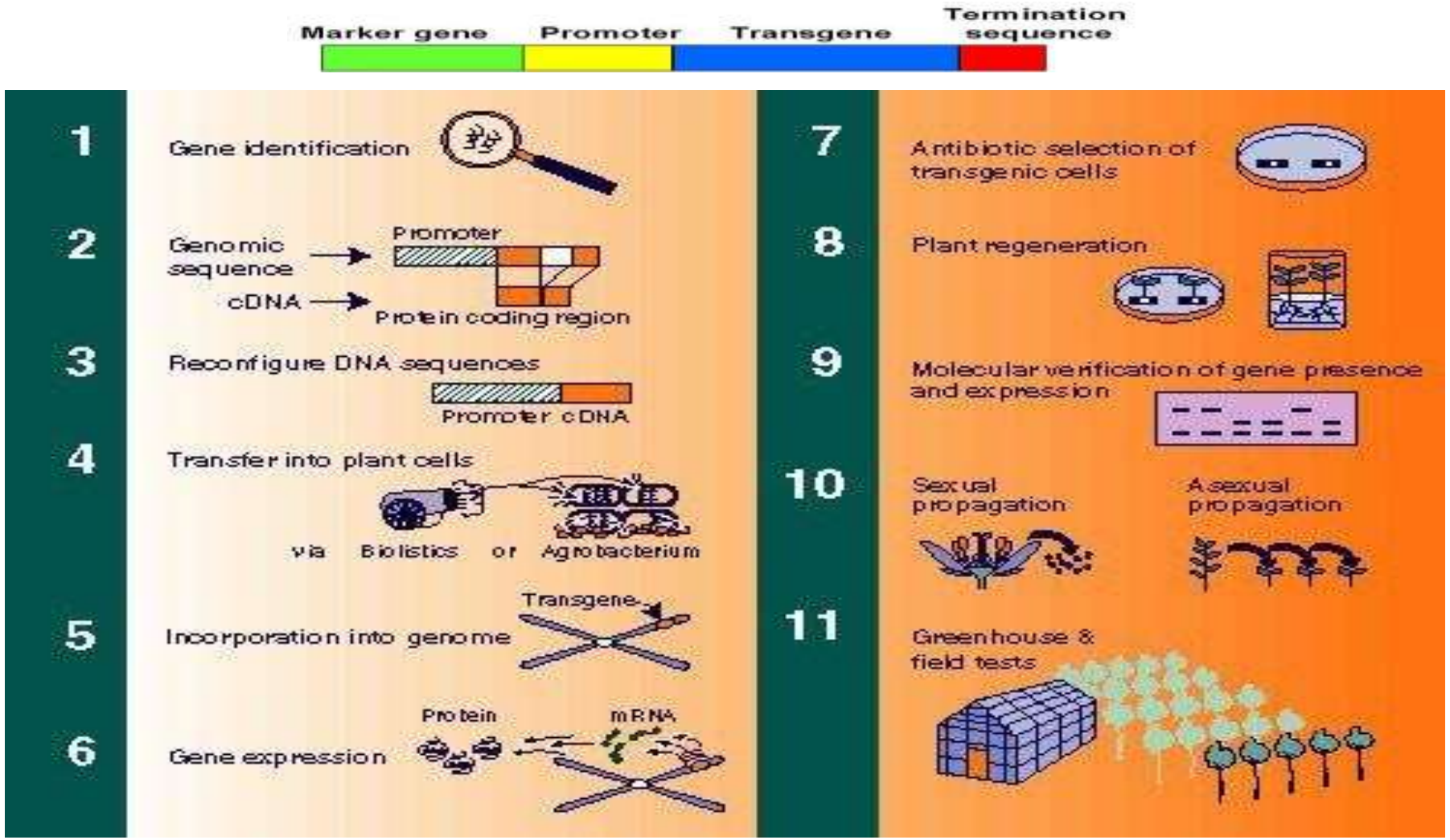

Therapeutic cloning
Egg cell
Body cell
Nucleus removed
Nucleus removed
Nucleus from the body cell inserted into egg cell
Cloned cell induced to form an embryo
Stem cells harvested from embryo cells
Nuclear reprogramming
Skin cells
Genes inserted to induce reprogramming
Reprogrammed cells resemble embryonic stem cells
SOURCE: Science Media Centre

Horticultural cloning

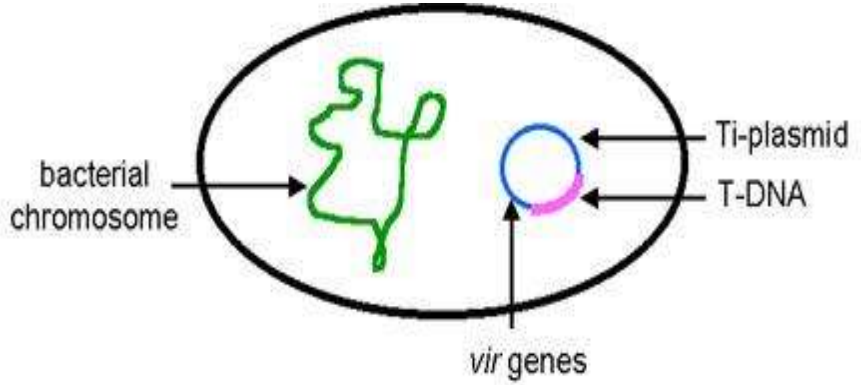
All plants which are originated from vegetativ reproductions are clones.
They have been derived from a single individual, multiplied by some process other than sexual reproduction.
Examples are bananas, grapes and potatoes.

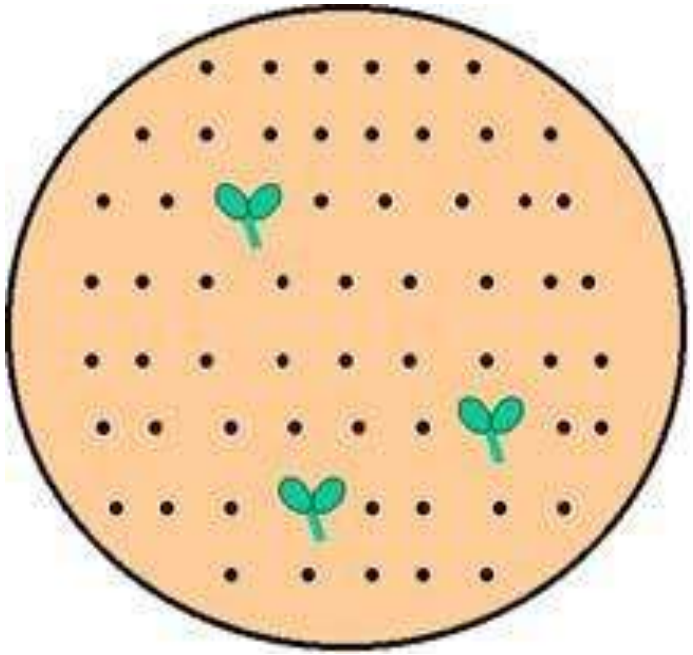


GM plants, Tranferring traits in ways which are not used in nature: GMOs

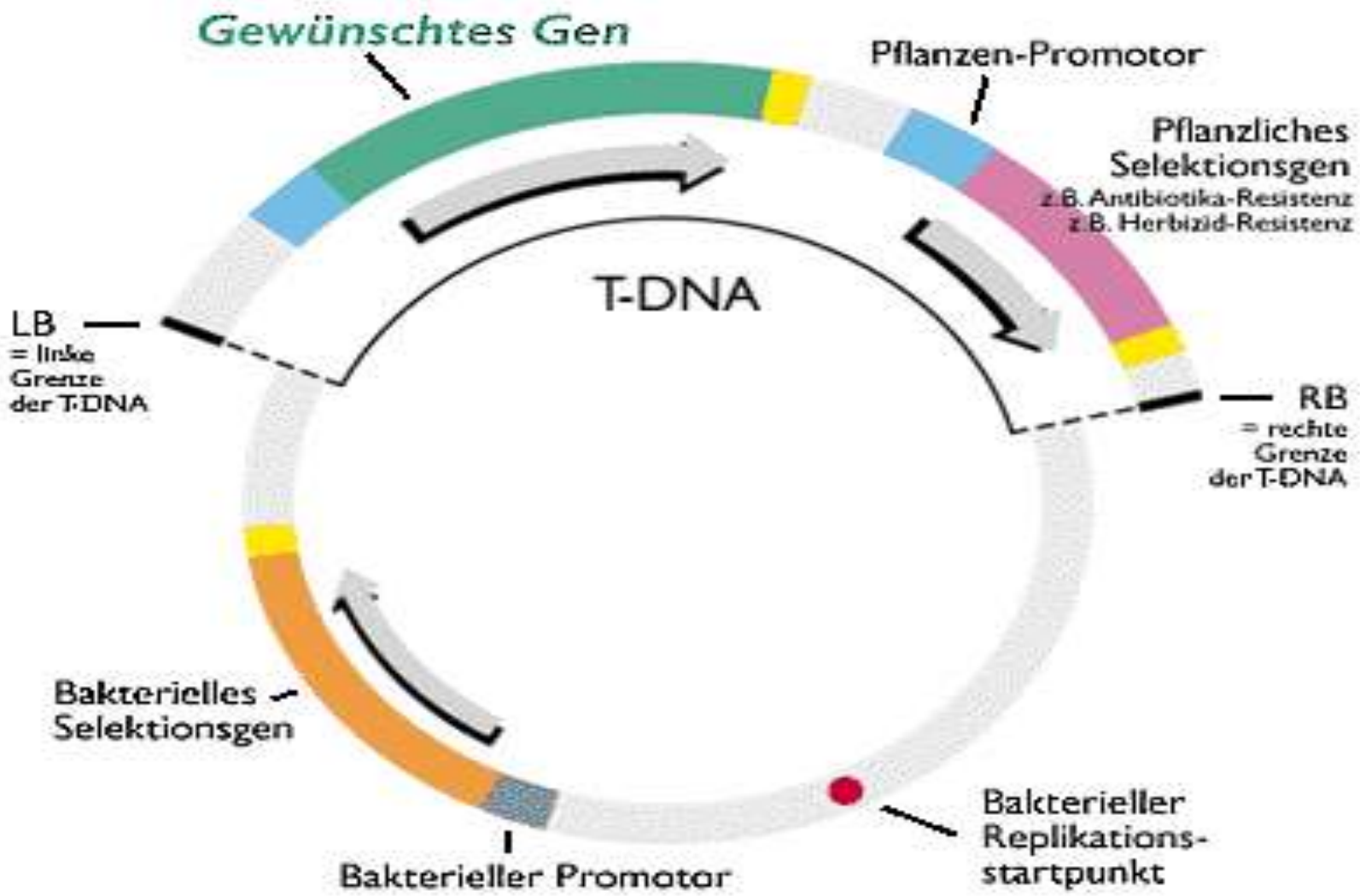


Agrobact. tumefaciens

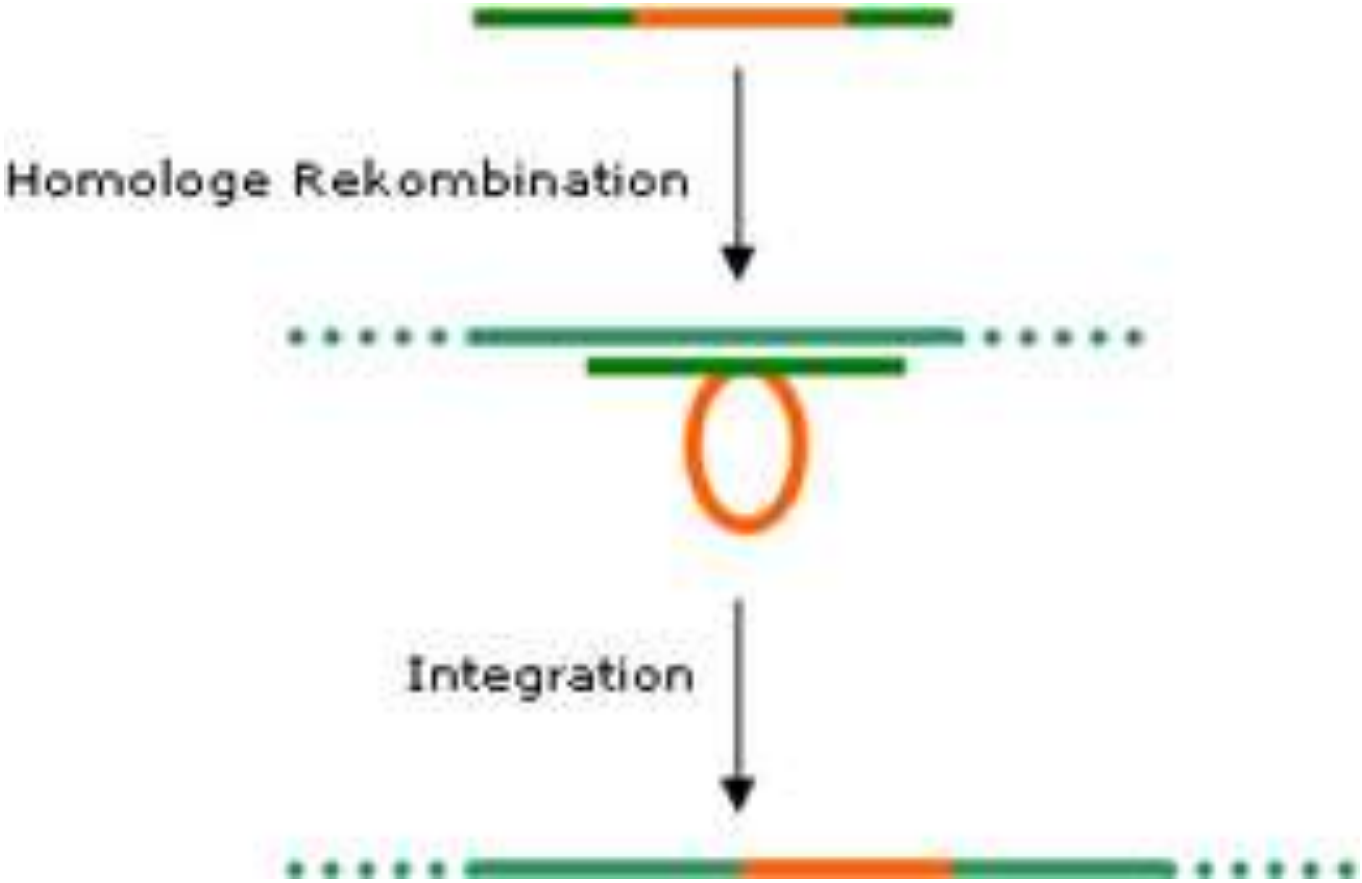




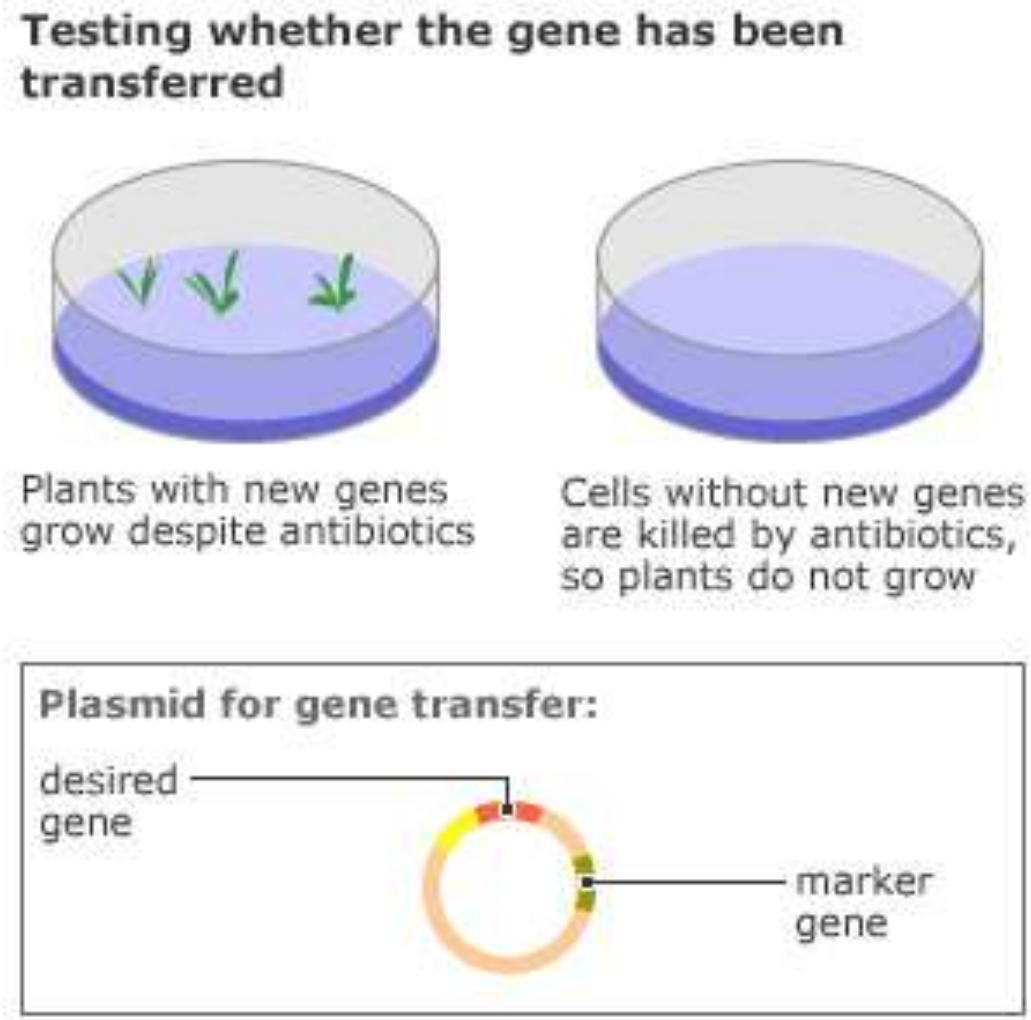
T DNA


Gewünschtes Gen
Pflanzen-Promotor
Pflanzliches Selektionsgen
z.B. Antibiotika-Resistenz
z.B. Herbizid-Resistenz
T-DNA
LB
= linke Grenze der T-DNA
RB
= rechte Grenze der T-DNA
Bakterielles Selektionsgen
Bakterieller Promotor
Bakterieller Replikations-startpunkt

Homologic recombination

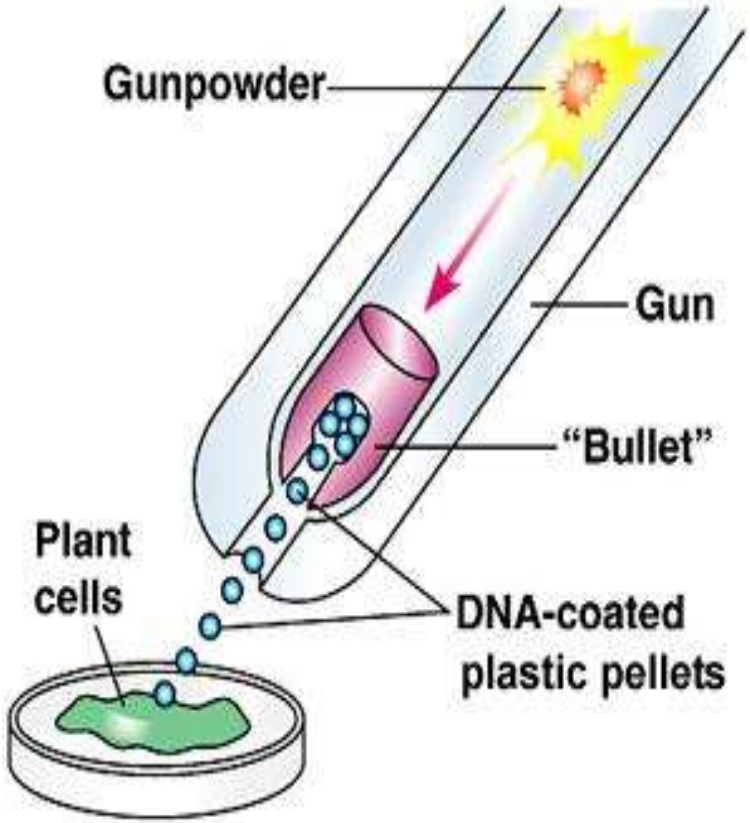


Antibiotic resistance marker gene



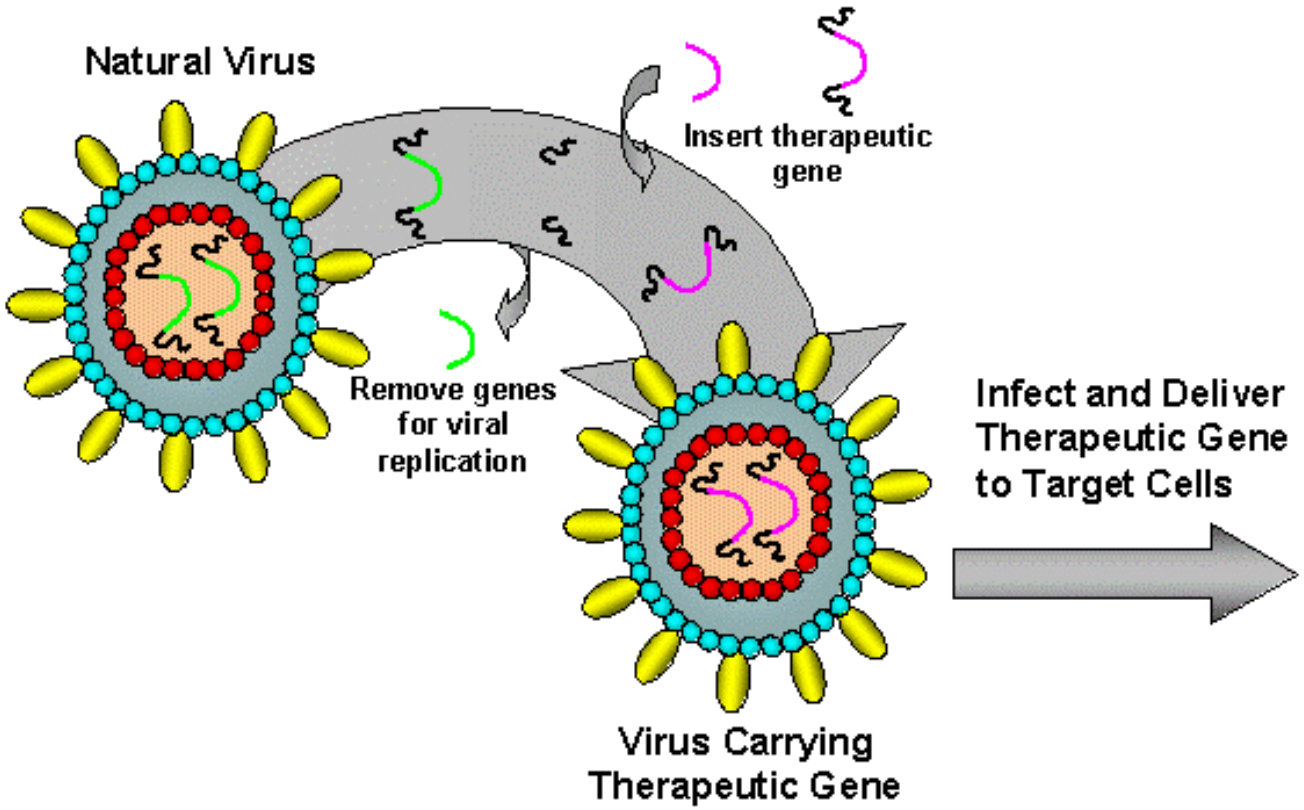
Gene gun

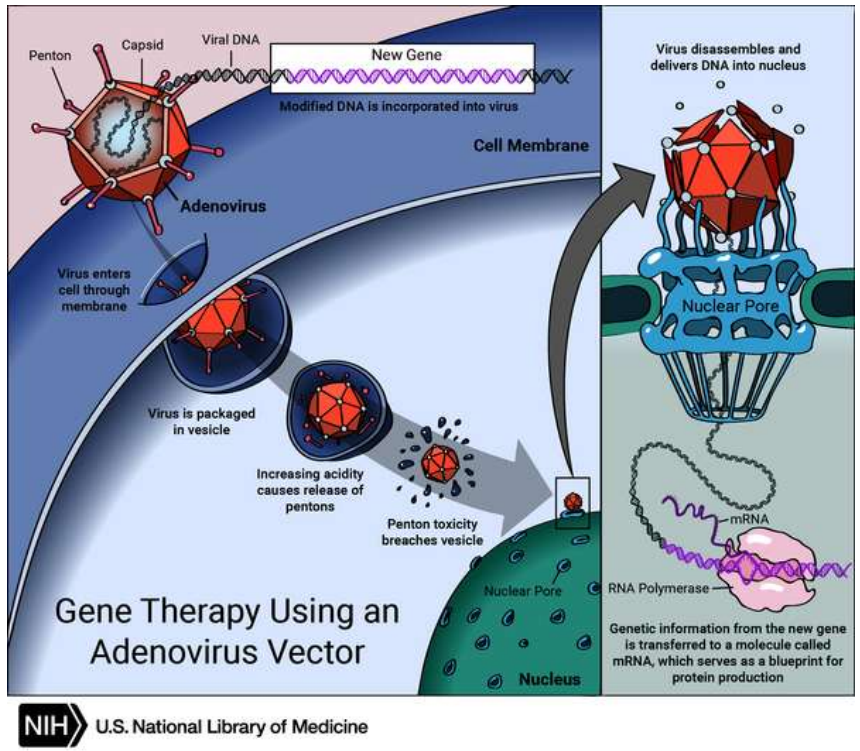
(a)



(b)

Gene transfer with viruses



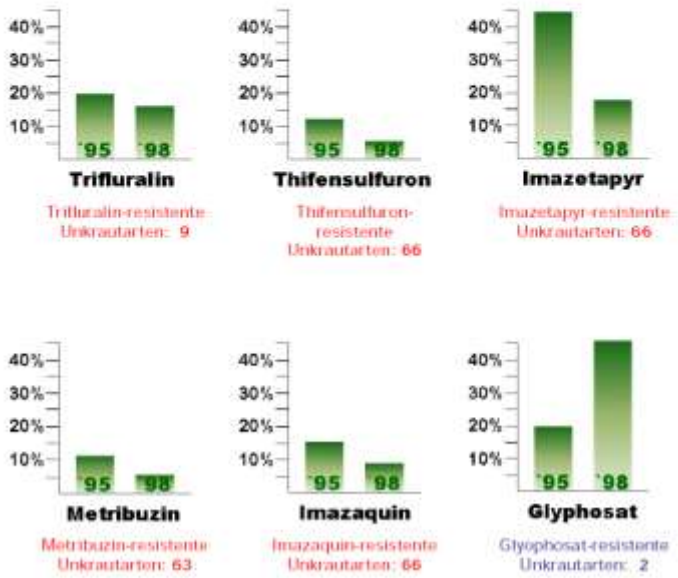


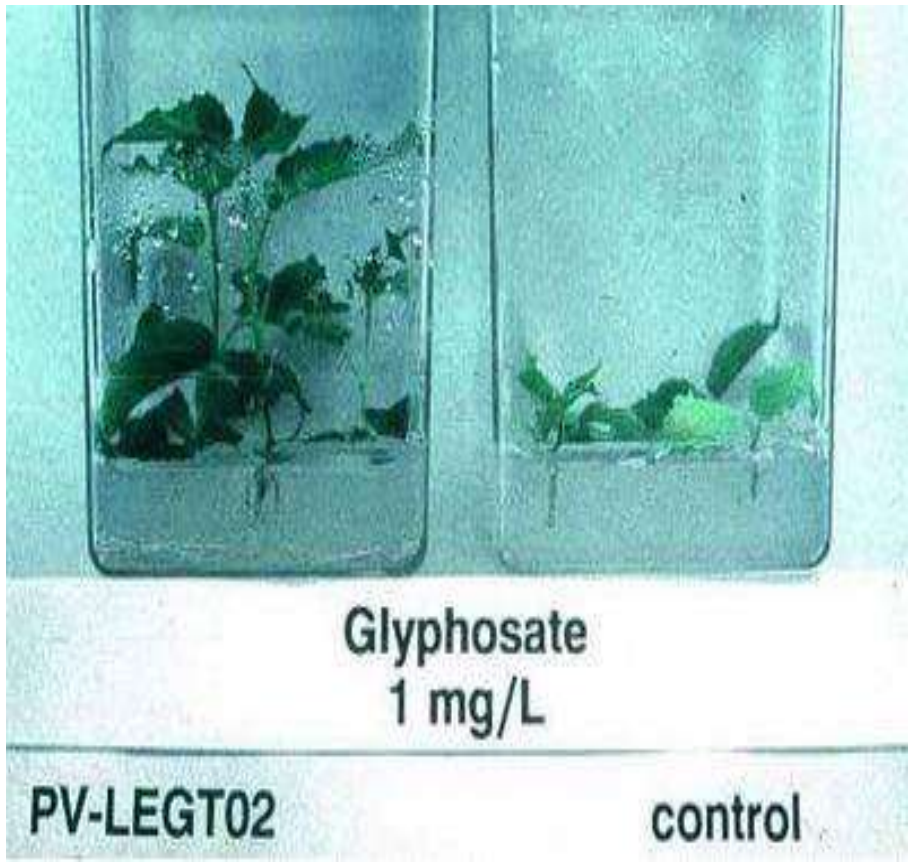
Main GMOs, Herbicide tolerance, glyphosate

Dank gentechnisch erzeugten Glyphosat-toleranten (Roundup-Ready) Sojasorten ist der Einsatz von problematischen Herbiziden im Sojaanbau seit 1995 rückläufig

Die Saulen repräsentieren den Anteil der US-Amerikanischen Sojaanbaufläche, auf welcher das betreffende Herbizid in den Jahren 1995 und 1998 eingesetzt wurde

Quellen: Gianessi und Carpenter, 2000 (http://www.ncfap.org/soy85.pdf);
International Survey of herbicide-resistant weeds (http://www.weedscience.com/default.htm)





Herbicide Resistant Soybean

BEFORE

AFTER

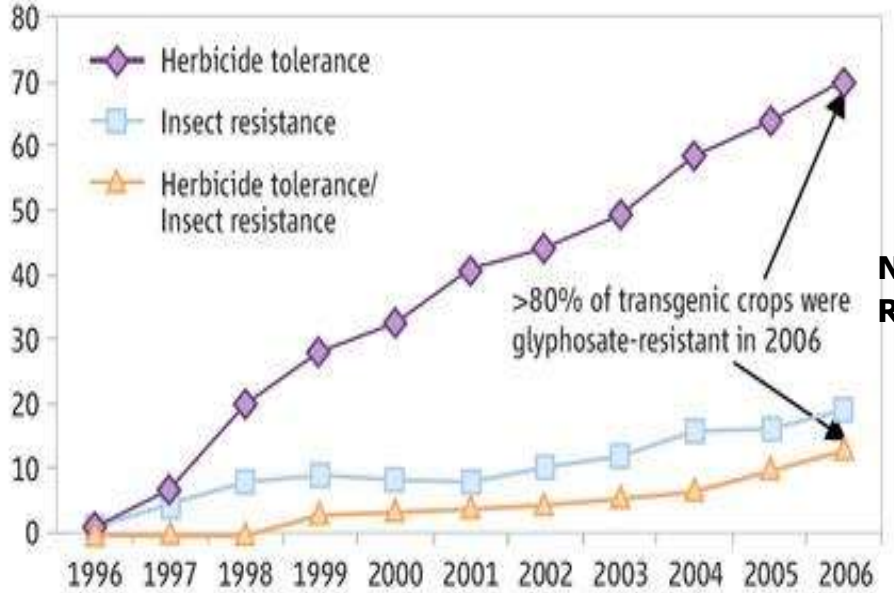
HERBICIDE APPLICATION

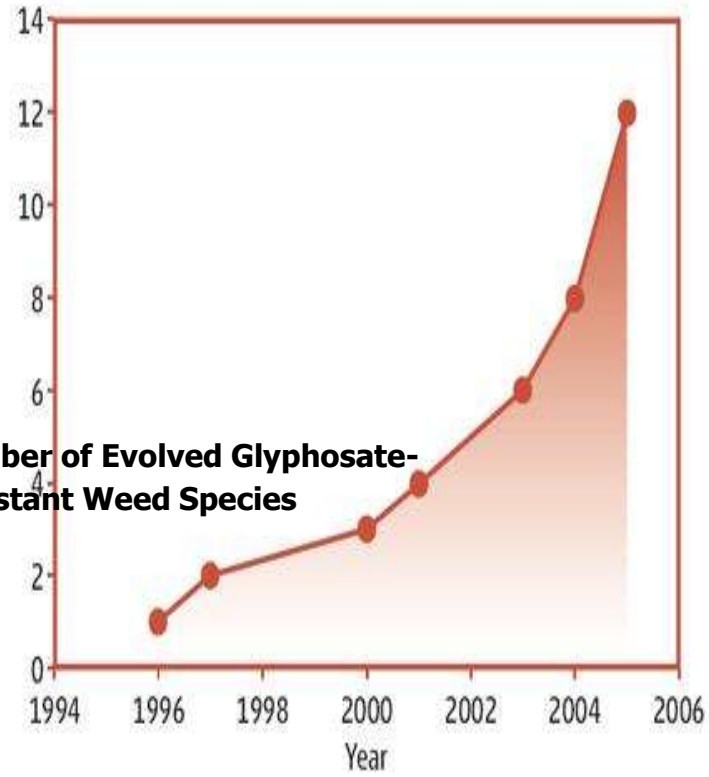
Herbicide Resistance: more or less herbicide? depending on local agricultural background

- Roundup Ready Soy, Corn, Canola
- Allows post-emergence herbicide spraying
- Increases yield
- Facilitates no-till farming
- 89% U.S. Soy crop (2006)

Old and new Problems: Resistance

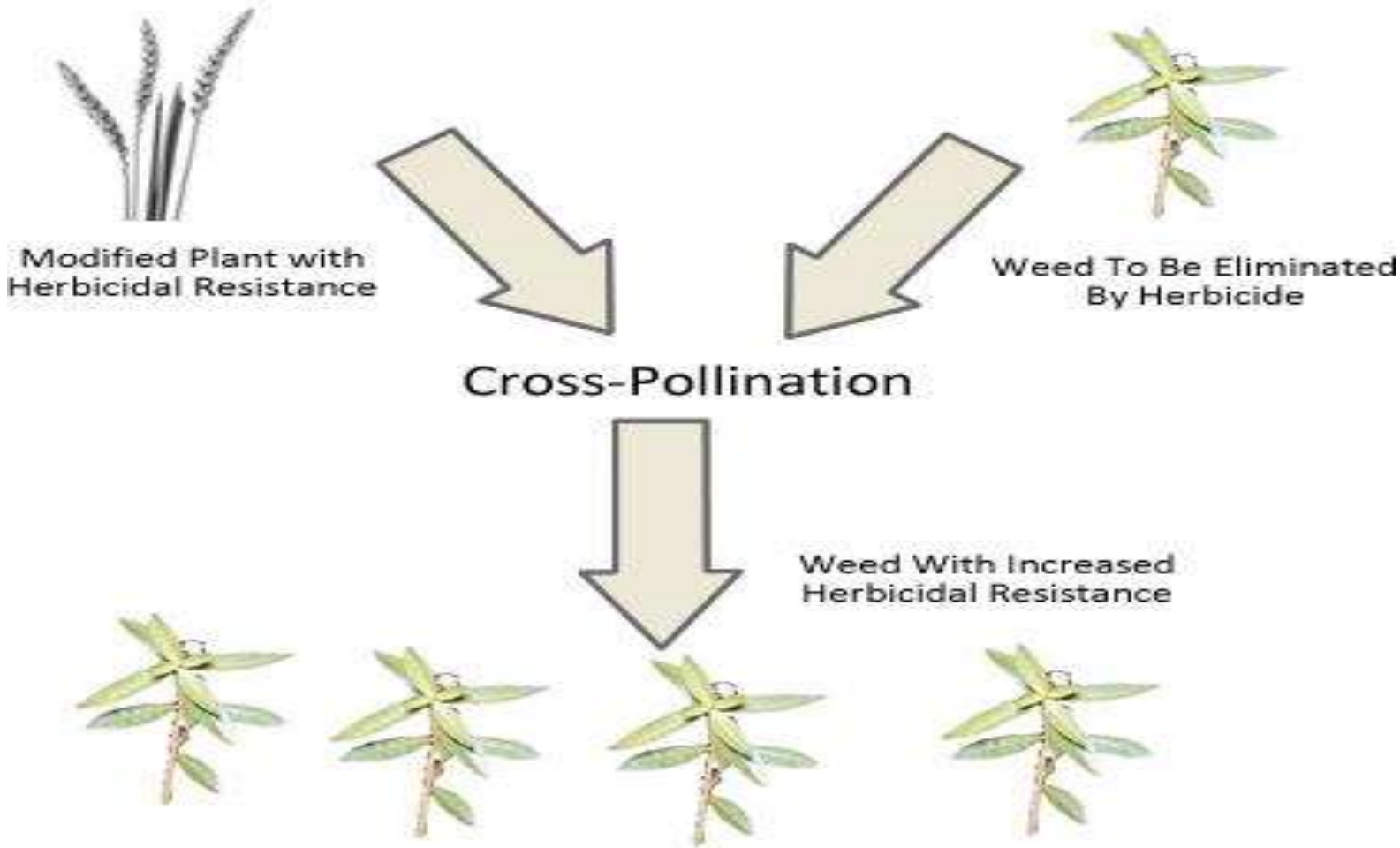
Herbicide Resistant Weeds Evolve





Number of Evolved Glyphosate-Resistant Weed Species

Herbizide resistance, gene transfer



Gene flow: multiresistant Rape

Environ. Biosafety Res. 5 (2006) 77–87
© ISBR, EDP Sciences, 2006
DOI: 10.1051/ebr:2006017

Detection of feral transgenic oilseed rape with multiple-herbicide resistance in Japan

Mitsuko AONO[1]*, Seiji WAKIYAMA[2], Masato NAGATSU[2], Nobuyoshi NAKAJIMA[1], Masanori TAMAOKI[1], Akihiro KUBO[1] and Hikaru SAJI[1]

[1]Environmental Biology Division, National Institute for Environmental Studies, 16-2 Onogawa, Tsukuba, 305-8506, Japan
[2]Japan Wildlife Research Center, 3-10-10 Shitaya, Taito-Ku, Tokyo, 110-8676, Japan

Repeated monitoring for escaped transgenic crop plants is sometimes necessary, especially in cases when the crop has not been approved for release into the environment. Transgenic oilseed rape (*Brassica napus*) was detected along roadsides in central Japan in a previous study. The goal of the current study was to monitor the distribution of transgenic oilseed rape and occurrence of hybridization of transgenic *B. napus* with feral populations of its closely related species (*B. rapa* and *B. juncea*) in the west of Japan in 2005. The progenies of 50 *B. napus*, 82 *B. rapa* and 283 *B. juncea* maternal plants from 95 sampling sites in seven port areas were screened for herbicide-resistance. Transgenic herbicide-resistant seeds were detected from 12 *B. napus* maternal plants growing at seven sampling sites in two port areas. A portion of the progeny from two transgenic *B. napus* plants had both glyphosate-resistance and glufosinate-resistance transgenes. Therefore, two types of transgenic *B. napus* plants are likely to have outcrossed with each other, since the double-herbicide-resistant transgenic strain of oilseed rape has not been developed intentionally for commercial purposes. As found in the previous study, no transgenic seeds were detected from *B. rapa* or *B. juncea*, and more extensive sampling is needed to determine whether introgression into these wild species has occurred.

Keywords: *Brassica* / establishment / glufosinate / glyphosate / herbicide / introgression / outcrossing / transgenic plant

Insect resistance, BT maize

BT resistance: B. thuringiensis proteins

Insect Resistant Maize

Corn hybrid with a Bt gene (left) and a hybrid susceptible to European corn borer (right).
Source: Monsanto

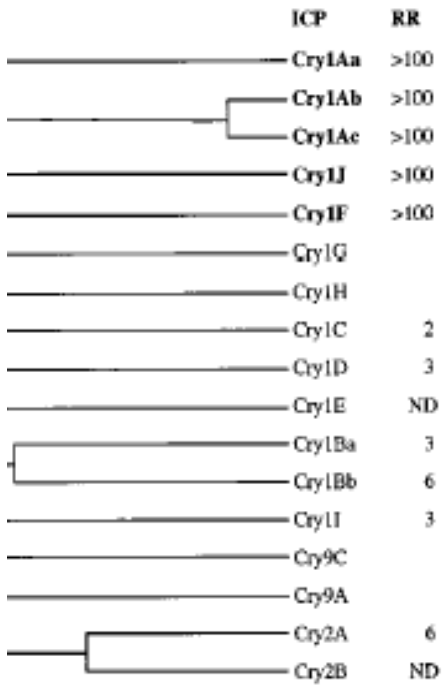


FIG. 1. Amino acid sequence similarity of domain II of *B. thuringiensis* toxins and resistance ratios (RR) of diamondback moth larvae. The dendrogram was

Roundup ready, Monsanto

Maiszünsler: wirtschaftlich bedeutendster Maisschädling

Es gibt mehrere Strategien zur Bekämpfung des Maiszünslers:

- **mechanisch durch Zerkleinern und Unterpflügen der auf dem Feld verbliebenen Pflanzenreste**
- **chemisch durch Einsatz von Insektiziden**
- **biologisch mit Hilfe von Trichogramma (Schlupfwespen)**
- **BT Toxin Präparate**
- **gentechnisch vermittelte Insektenresistenz besitzt (Bt-Mais)**

Bt Corn

- Natural insecticide from *Bacillus thuringiensis*
- Non-toxic to humans
- Target insect: corn borer
- Potential to:
  - reduce insecticide use
  - reduce mycotoxins
- 40% U.S. Corn crop Bt (2006)

Bt Concerns

- Bt pollen harms non-target species?
- Bt crops select for resistant insects
- Bt pollen can drift to organic fields
- Food system failed to keep BT Starlink corn out of human food products

Disease Resistance, viruses

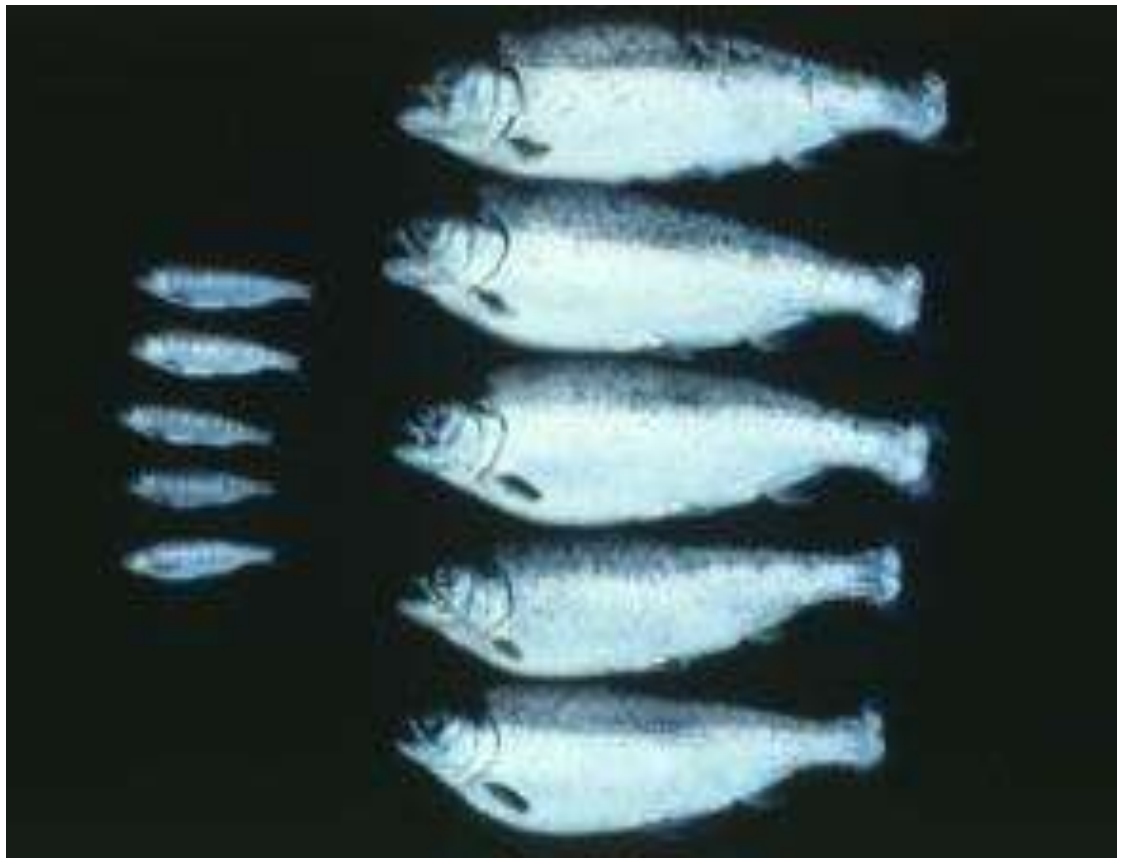
.

Genetically engineered papaya resistant papaya ringspot virus

- **Cantaloupes**
- **Cucumbers**
- **Corn**
- **Rice**
- **Papaya**
- **Potatoes**
- **Soybeans**
- **Squash**
- **Tomatoes**
- **Wheat**

Growth-enhanced fish

Salmon Growth hormone expressed in cold waters & unlinked from seasonal temp.



Auto-transgenic mud loach: β-actin promoter linked to GH gene.

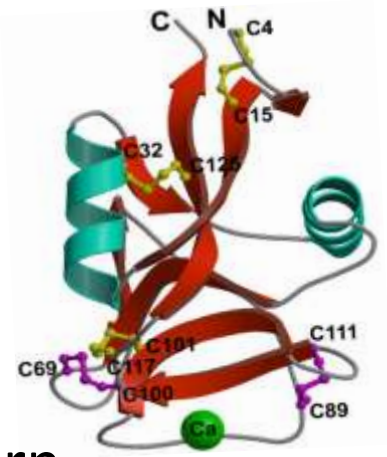
(Devlin et al. 1994)

GM Salmon

- Probleme der Lachsindustrie
- gv Lachs von Aqua Bounty
- Produktionssteigerung über Ernährung, Krankheitsresistenz

- Gefahr für die Wildlachspopulationen
- Abhängigkeit des Fischfutters
- Umweltverschmutzung durch Lachszucht

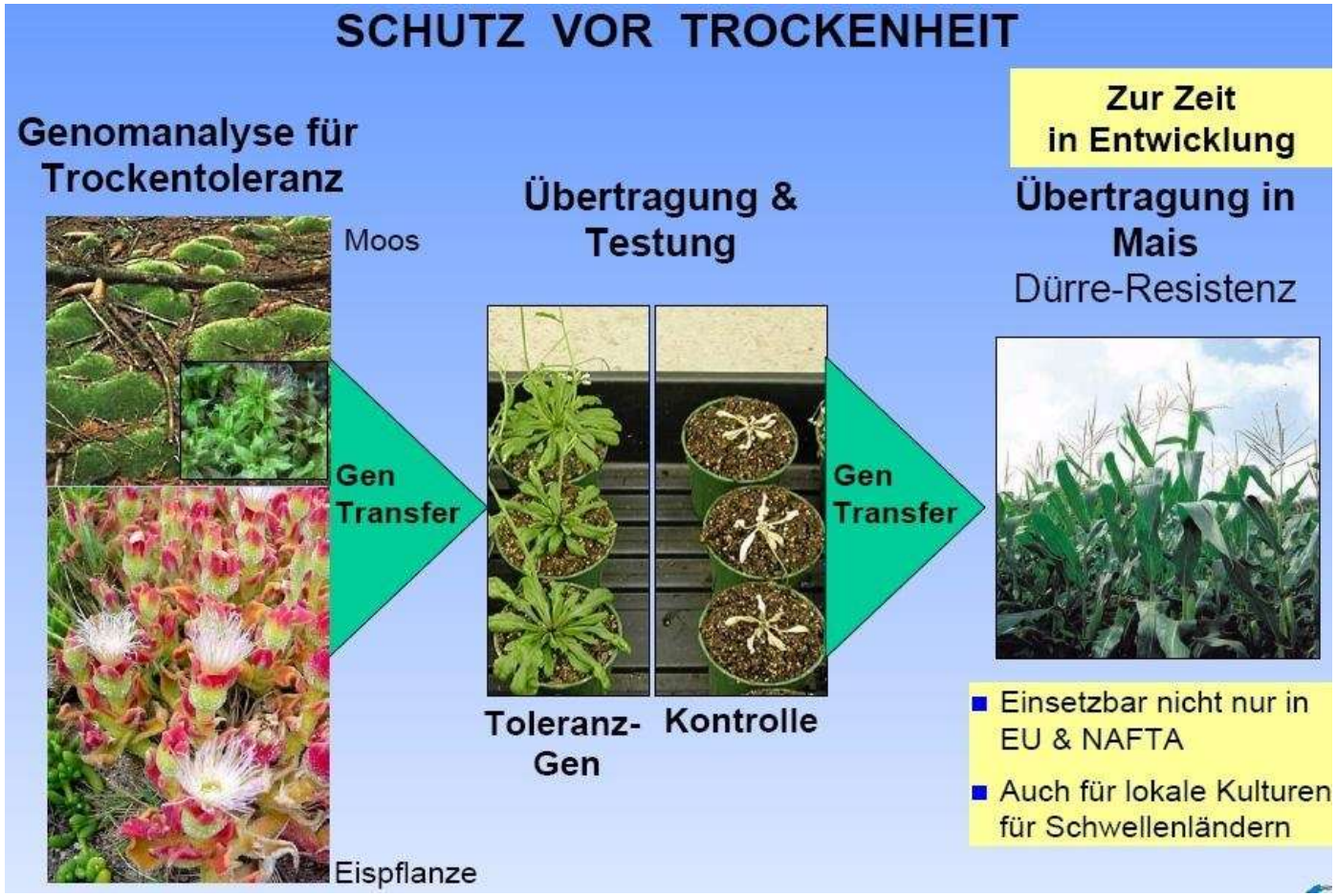
- Atlantischer Lachs von Aqua Bounty
- **Wachstumshormon-Gen** des Chinook Lachs
- **Frostschutz-Protein-Gen**
- bessere Entwicklung in kalten kanadischen Gewässern
- Wachstum über das ganze Jahr
- normales Gewicht in der Hälfte der Zeit erreicht



BELFOND-CURIEUX, O.L et al.: Factors to consider before production and commercialization of aquatic genetically modified organisms: the case of transgenic salmon; Environmental Science & Policy 12; 170-189; 2009.

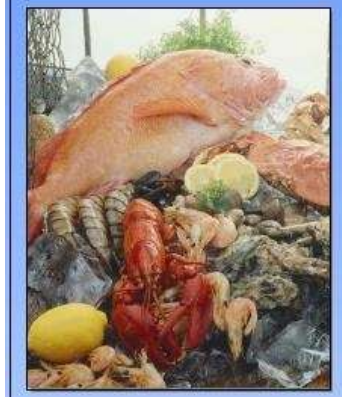
GMO tobacco,
expression of human proteins in plants

GMOs in development:
CLAIMED BREEDING OBJECTIVES



CLAIMED BREEDING OBJECTIVES

GESUNDE ERNÄHRUNG



Omega-3-Fettsäuren zur Vorbeugung von Herz-Kreislauf Erkrankungen

- Empfehlung der Deutschen Herzstiftung: **1-2 Gramm Omega-3 Fettsäure pro Tag**
- Bislang konventionelle Quelle: **Fisch und Meeresfrüchte**

Die verfügbare Menge an Fisch und Meeresfrüchten ist begrenzt.

Produktion in der Pflanze in Entwicklung

In Entwicklung & Feldversuche

Vorteile der Pflanze

- Höhere Produktqualität
- Umweltschonendes Herstellungsverfahren
- Kostengünstige Produktion
- Ausreichend verfügbar

Claimed breeding objectives

VERRINGERUNG VON ALLERGENEN & GIFTEN

Weizen, Mais, Reis: Gluten-frei — In Entwicklung

Blockade der Gene für Gluten-Produktion

Ziel: Risikofreier Konsum für Zöliakie-Patienten

Erdnuss — In Entwicklung

Unterdrückung der Synthese von Allergie-auslösenden Proteinen

Maniok (Cassava): Linamarin-Reduktion

Blockade der Gene für Linamarin-Produktion

Linamarin wird in Blausäure umgewandelt und kann so zu Vergiftungen führen — In Entwicklung

BREEDING OBJECTIVES

PFLANZEN ZUR BIO-PRODUKTION

Gentechnisch veränderte Stärkekartoffel für technische Anwendungen

Feldversuche

Was wurde geändert ?

Ein Gen, für ein Merkmal (Stärke), wurde abgeschaltet

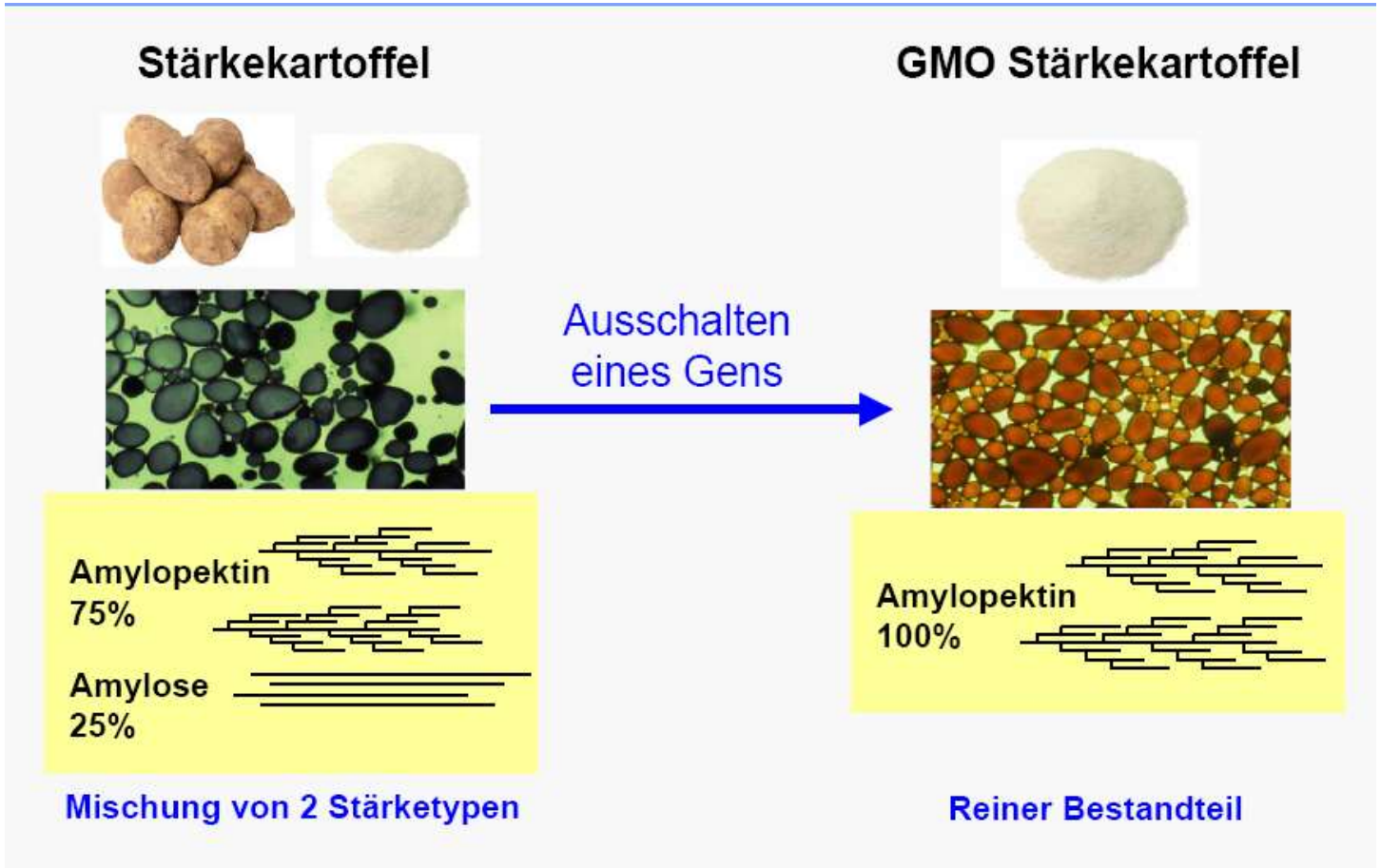
Ergebnis

Knollen, die veränderte & optimierte Stärke enthalten

Vorteile der optimierten Stärke

- Verbesserte Produktqualität
- Optimierung von Produktionsprozessen
- Einsparung von Energie und Ressourcen
- Ersatz von synthetischen nicht-abbaubaren Produkten

Breeding objectives



GMO Trees

Living on EARTH

THIS WEEK'S SHOW

GMO-Trees

Air Date: Week of May 29, 2009

THIS WEEK'S SHOW
ABOUT LIVING ON EARTH
WHERE TO TUNE IN
LOE EDUCATION PROGRAM
TAPES & OTHER PRODUCTS
ARCHIVES
BOOKS AND MUSIC
FOR STATIONS
SPECIAL FEATURES
STORY IDEAS?
NEWSLETTER SIGN-UP
SEARCH
STUDIO RENTALS

RealAudio for this Story
(Requires RealPlayer)

Download this Story
(mp3 format)

Links Related to this Story

Maria Tesorera, from a women's group in Chile, protests outside the Belgian Permanent Mission in New York City. Belgium recently planted a test plot of genetically engineered low-ligning poplar trees. (Orin Langelle)

Scientists are developing genetically modified trees for the forests of the future. Ann Peterman of the Global

Living on Earth is an independent media program and relies entirely on contributions from listeners and institutions supporting public service. Please donate

GENETICALLY MODIFIED TREES: PRODUCTION, PROPERTIES, AND POTENTIAL

by Kevan M.A. Gartland[1], Robert M. Crow[1], Trevor M. Fenning[2], and Jill S. Gartland[1]

CONCLUSIONS

Tree genetic modification is most likely to be acceptable to the public in two areas: where greater productivity from reduced plantation forest areas can be shown to increase areas left to nature's own devices, and in restoring threatened trees to damaged landscapes, such as the elm. Whichever aspects of GM trees advance most rapidly in the future, environmental risk assessment should always be carried out, on a case-by-case basis, until a sufficient body of knowledge on the anticipated benefits and the possible risks of this exciting technology is established.

GM FLowers

Auto Toyota Turns to GMO Flowers to Relieve it of Prius Manufacturing Pollution

Source: DailyTech DT • October 30, 2009 4 retweet Share

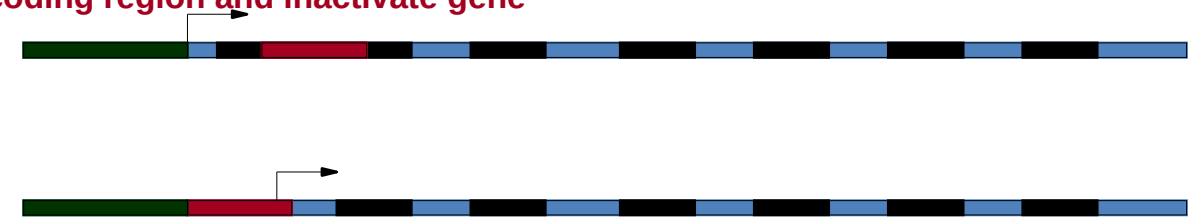
A rather unusual way of rectifying manufacturing emissions has been developed by the world's leading automaker.

Are you overcome with guilt about how much carbon, sulfides, nitrides, and other emissions goodies were pumped into the atmosphere in the making of your new Toyota Prius? Do you feel dirty?

Well, Toyota has just the thing for you. It has genetically engineered two new species of flowers that soak up air pollution.

Safety: Random integration, Insertional mutagenesis

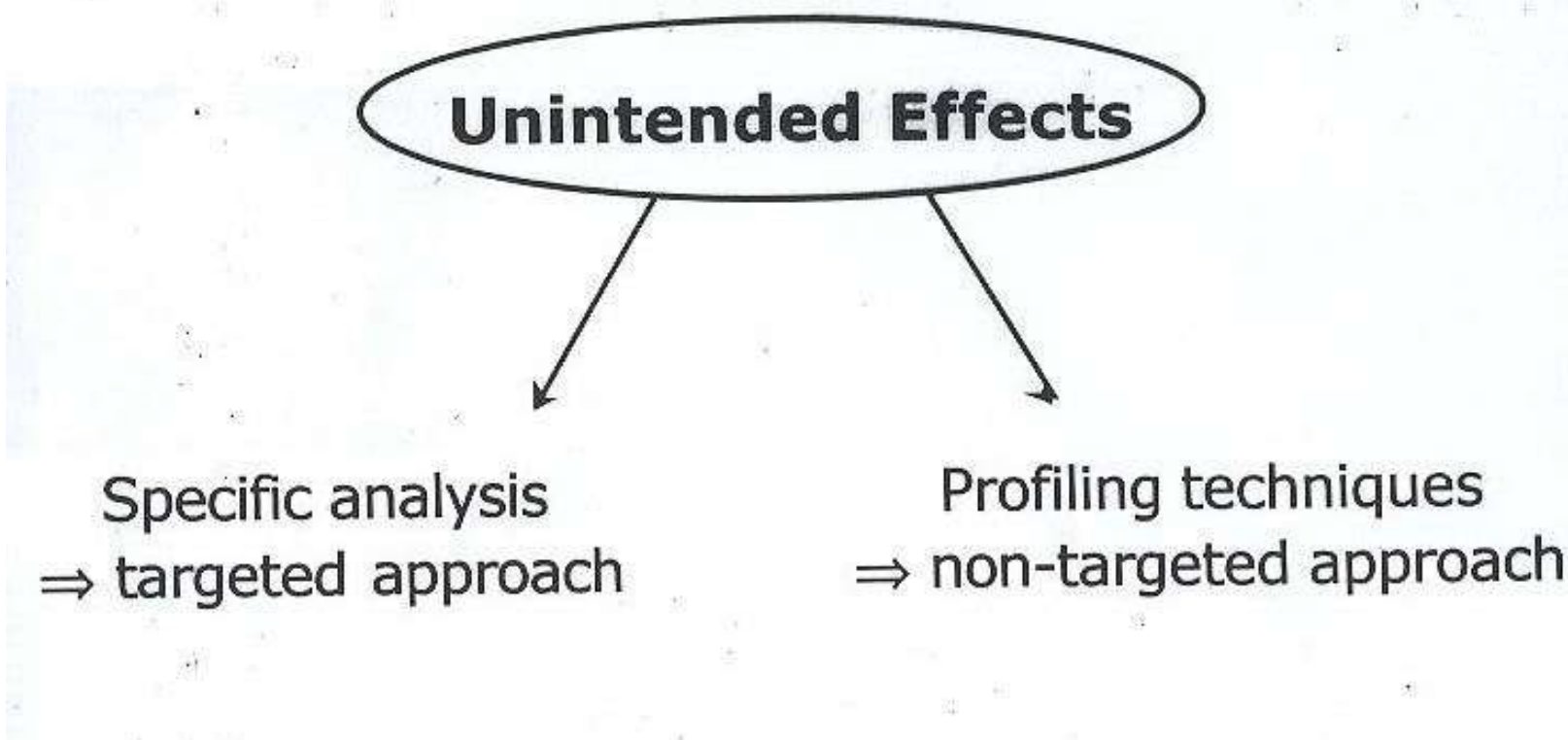
1. Interrupt coding region and inactivate gene



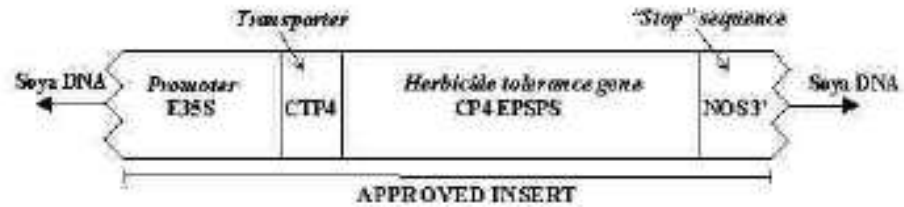
Vector

2. Insert next to gene and activate its expression inappropriately

Safety assessment of transgenic food



a) Approved DNA insert as described by Monsanto in their original EU application for marketing (from Monsanto, 2000)[3]. The function of each individual component of the insert is stated in italics.



b) Unapproved, multiple DNA inserts and unidentified DNA as now revealed (unapproved DNA is shaded). Two additional, unapproved inserts are present: a 250 base pair (bp) fragment of CP4 EPSPS attached to the main insert and a separate 72 bp insert of CP4 EPSPS (Monsanto, 2000)[3]. Adjacent to the unapproved 250 bp insert is the newly discovered (Windels et al. 2001)[4] 534 bp of unidentified, unapproved DNA.

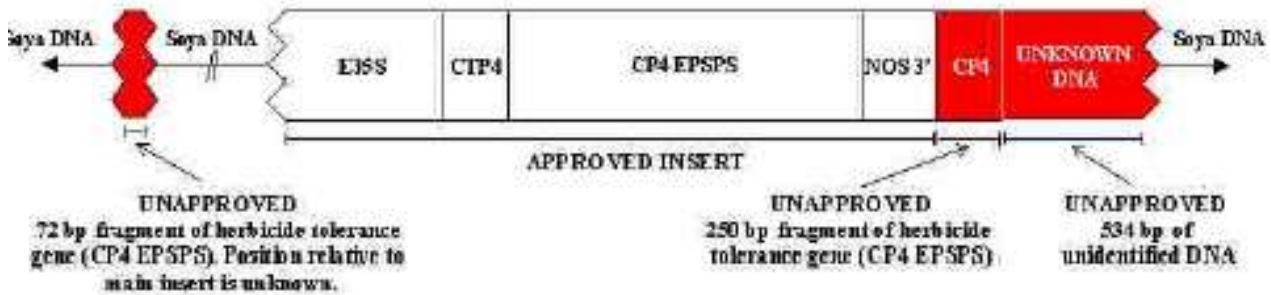


Figure Schematic of the DNA inserts in Monsanto's Roundup Ready soya. Abbreviations: bp - base pair, used to indicate the length of the DNA fragments[1]; E35S - cauliflower mosaic virus promoter; CTP4 - chloroplast transit peptide sequence from petunia; CP4 EPSPS - herbicide tolerance gene from *Agrobacterium sp.*, strain CP4; NOS 3' - untranslated region of nopaline synthase gene. For footnotes see main text.

Toxicology Asessment: Difficulties Animal Feeding Studies Whole Foods

Small doses to be fed (bulk, satiety)

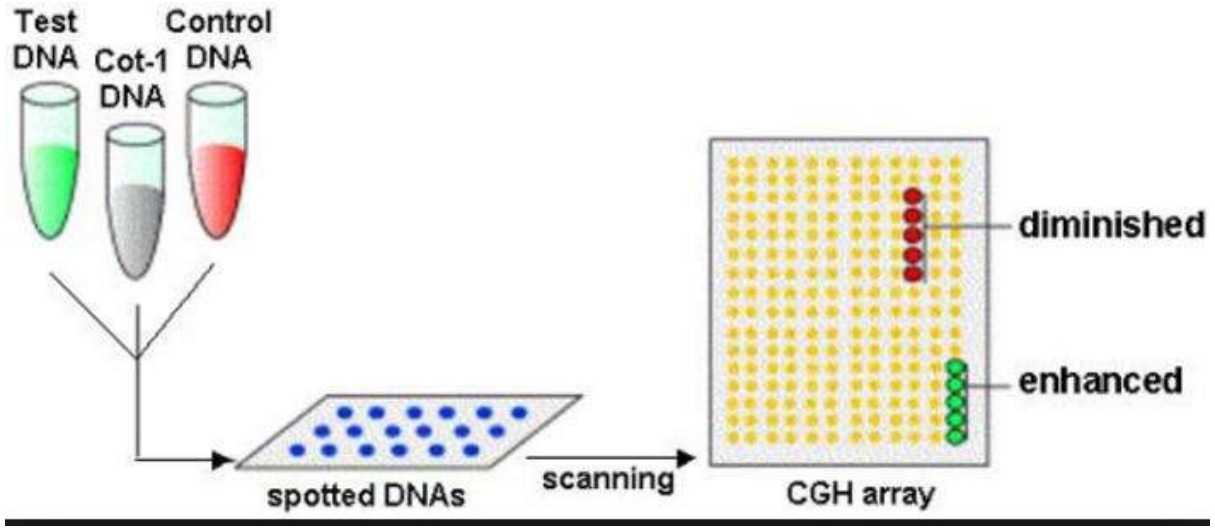
Nutritional imbalance of the diet

Many confounding factors

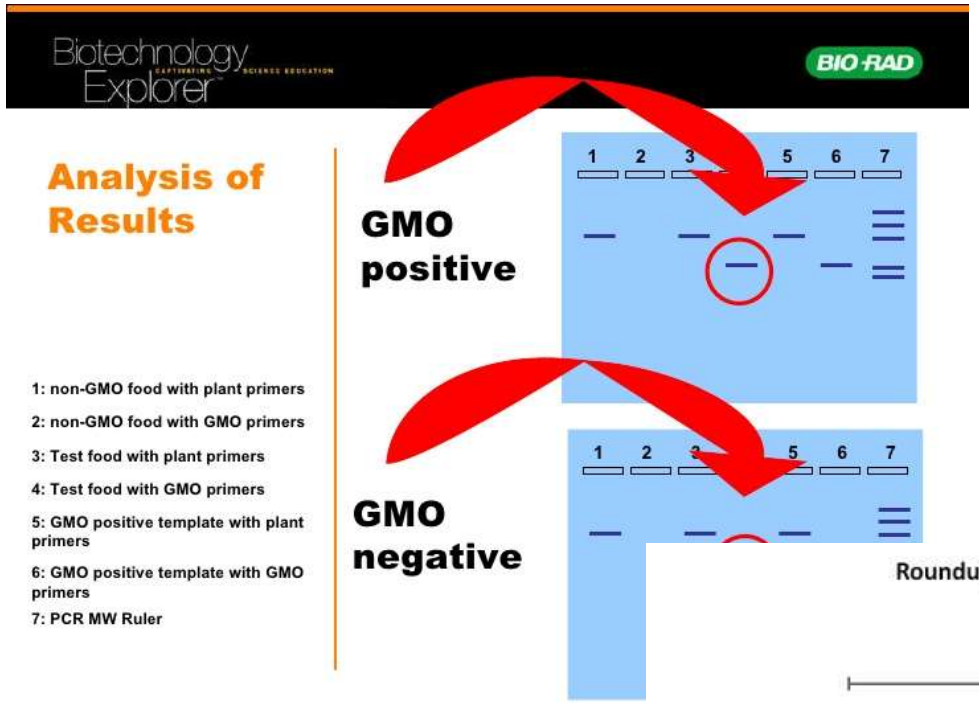
Small safety margins, if any

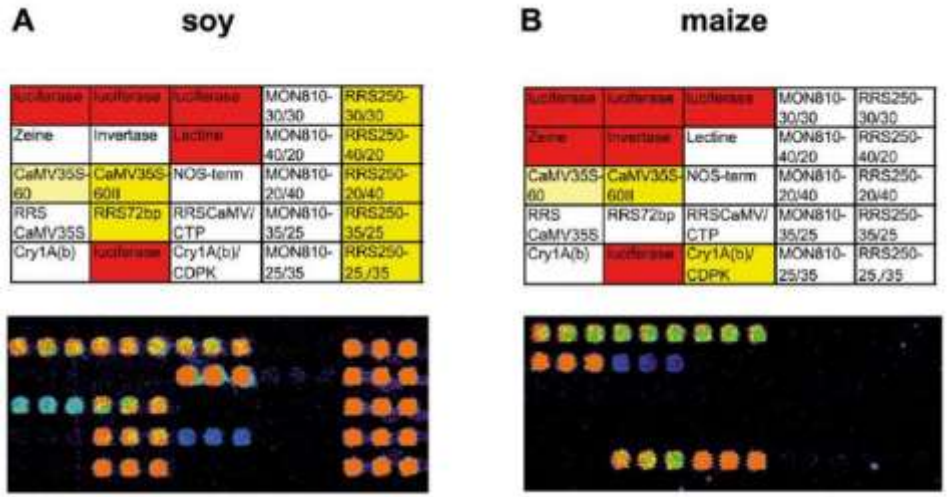
Insufficient sensitivity for specific endpoints

Detection of unintended effects in vitro, in vivo

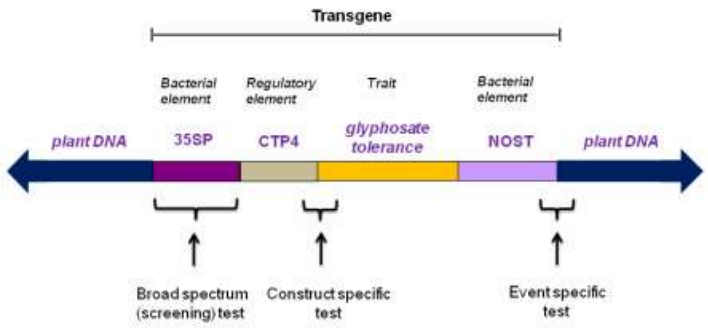


GMO tests: PCR, primers, areas, array





Roundup Ready soybean



New Objectives for gene transfer

Conventional Transgenic Approaches

Drawbacks:

- Random insertion of transgene
- Not suitable for gene targeting or precise gene mutation
- Difficult to perform gene replacement or create allelic variation
- Introduction of undesirable DNA fragments (T-DNA, selection markers)
- Extensive regulatory requirements
- Public concerns over transgenic crops

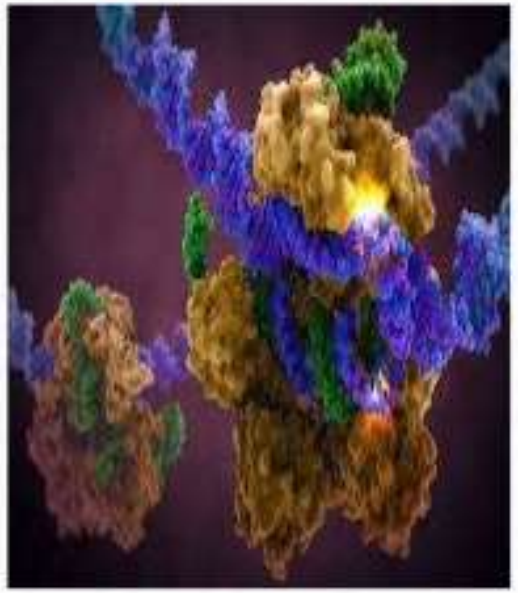
New technology is much needed:

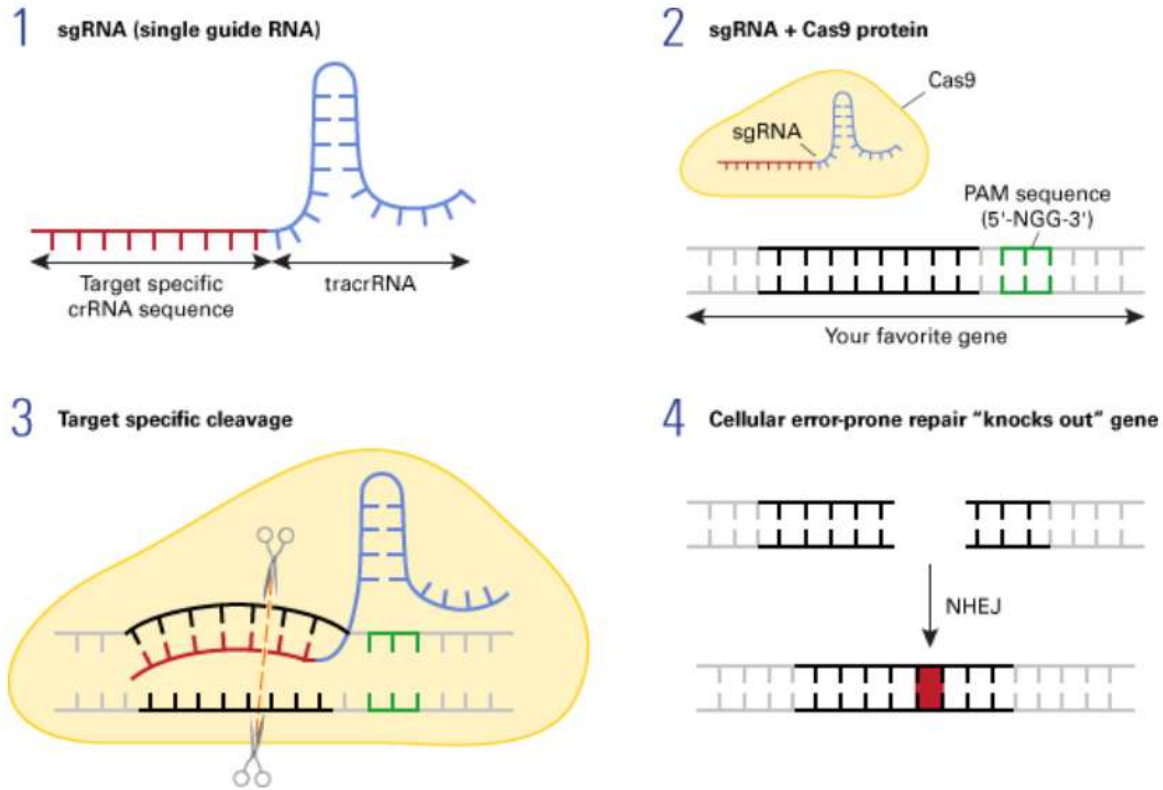
- To precisely and efficiently manipulate genome for crop improvement
- To reduce regulatory hurdles and public concerns

Gene editing

Cas-9 (**c**RISPR **a**ssociated **p**rotein 9)

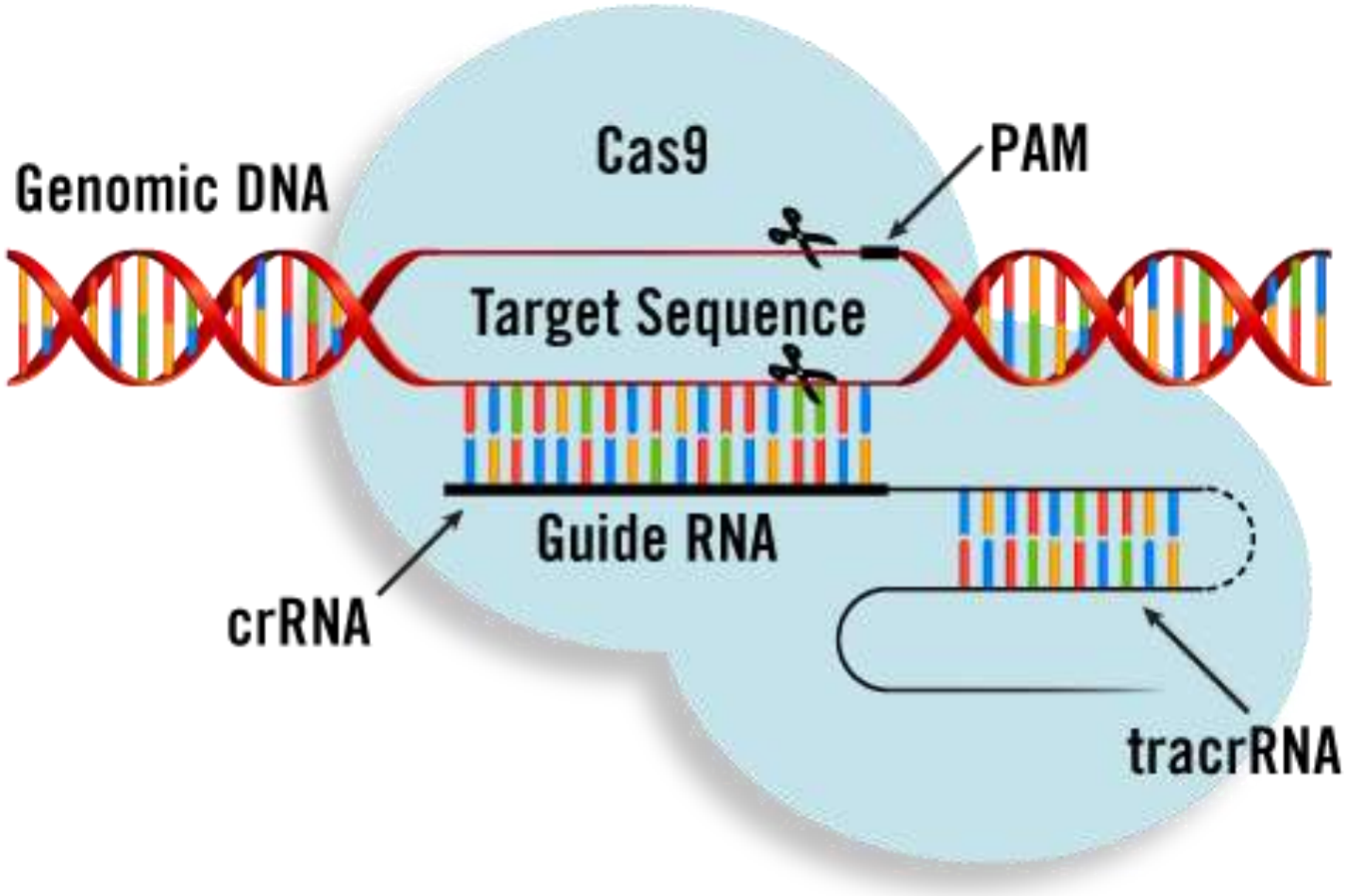
- is an RNA guided DNA endonucleases enzyme.
- associated with CRISPR
- which plays an role in adaptive immunity system, found in bacteria Streptococcus Pyogenes.
- involved in Type II CRISPR mechanism



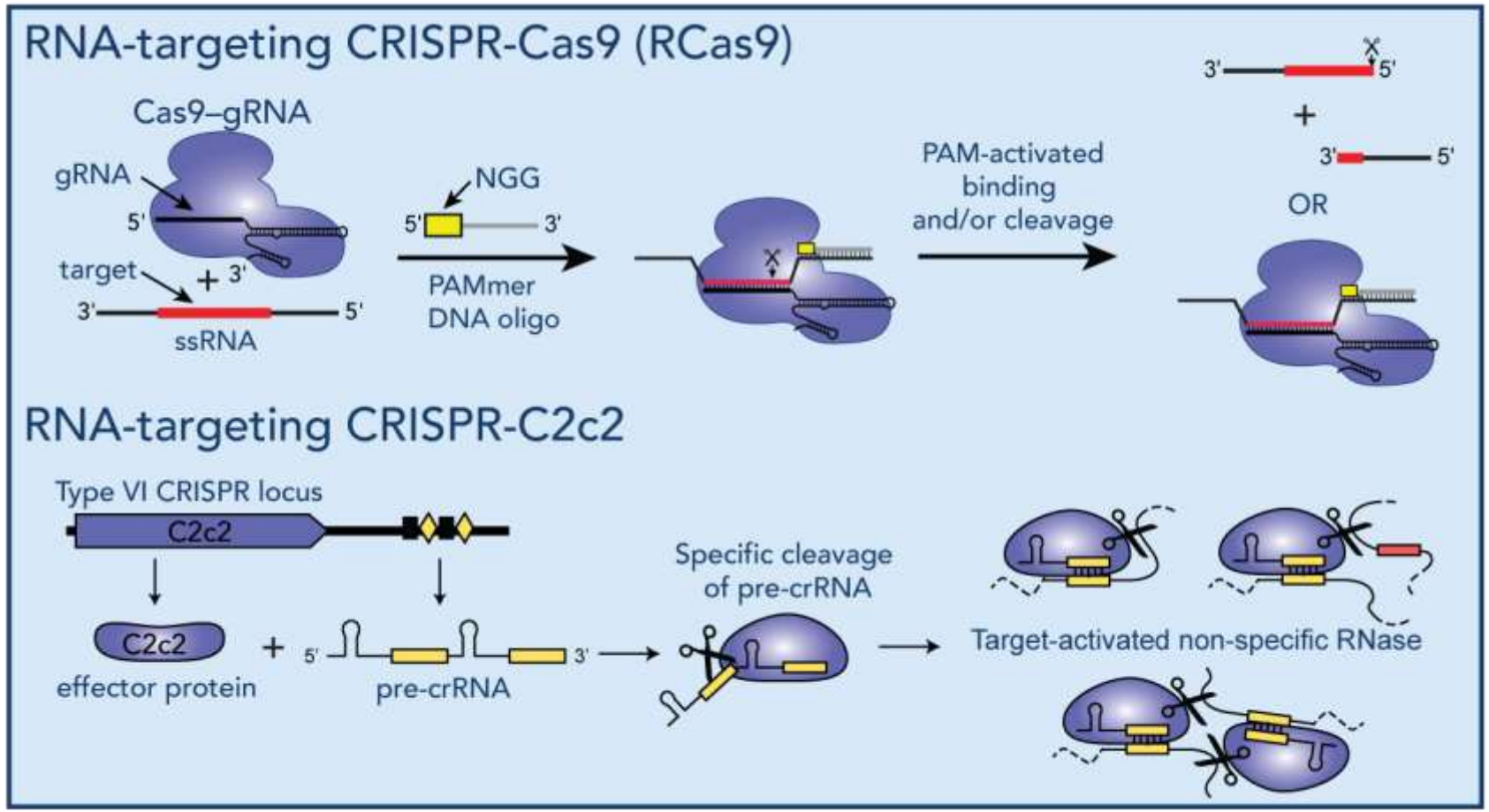


The principle of CRISPR/Cas9-mediated gene disruption. A single guide RNA (sgRNA), consisting of a crRNA sequence that is specific to the DNA target, and a tracrRNA sequence that interacts with the Cas9 protein (1), binds to a recombinant form of Cas9 protein that has DNA endonuclease activity (2). The resulting complex will cause target-specific double-stranded DNA cleavage (3). The cleavage site will be repaired by the nonhomologous end joining (NHEJ) DNA repair pathway, an error-prone process that may result in insertions/deletions (INDELs) that may disrupt gene function (4).

CRISPR/CAS9


Genomic DNA
Cas9
PAM
Target Sequence
Guide RNA
crRNA
tracrRNA

Targeting RNA



CRISPR-Cas9

Broad Application of CRISPR-Cas9 Technology

Technical advantages for basic plant biology and crop breeding

- Targeted gene mutation (multiple or redundant genes)
- Site-specific integration and gene stacking
- Gene replacement via homologous recombination
- Site-directed mutagenesis to create allelic variation
- Chromosomal engineering such as deletion or translocation
- Modification and labeling of multiple genomic sites
- Transcriptional modulation of multiple genes and pathways
- Epigenome editing such as methylation and demethylation
- Cisgenesis without introducing undesirable foreign DNA

Economic, regulatory and societal benefits:

- Reduce costs for precise and efficient molecular breeding
- Eliminate or significantly reduce regulatory requirements
- Alleviate public concerns about GM crops

CRISPR-Cas9, applications

Near-term Applications for Crop Breeding

1. Targeted deletion of single or multiple genes for transgene-free, mutational breeding in various crop species.

2. Site-specific integration and precise gene stacking for transgenic or cisgenic breeding.

3. Multiplex editing to create allelic variation at quantitative trait loci to improve multiple agronomic traits (yield, quality, disease resistance and abiotic stress tolerance).

Genome editing in rice for S918A conversion in *Pita*

			Amino Acid Position				
Rice Variety	Resistant with *AVR-Pita* Fungus	Rice Type	6	148	158	176	918
Yashiro-mochi	Yes	Japonica	I	R	H	D	A
Tetep	Yes	Indica	I	R	H	D	A
C101A51	No	Indica	I	R	H	D	S
Tsuyuake	No	Japonica	S	S	Q	V	S

Table after Bryan et al. (2000), The Plant Cell

Video gene editing

Genome editing is going to be high on next Parliament agenda, MEP says

By Gerardo Fortuna | EURACTIV.com 28. März 2019 (updated: 1. Apr. 2019)

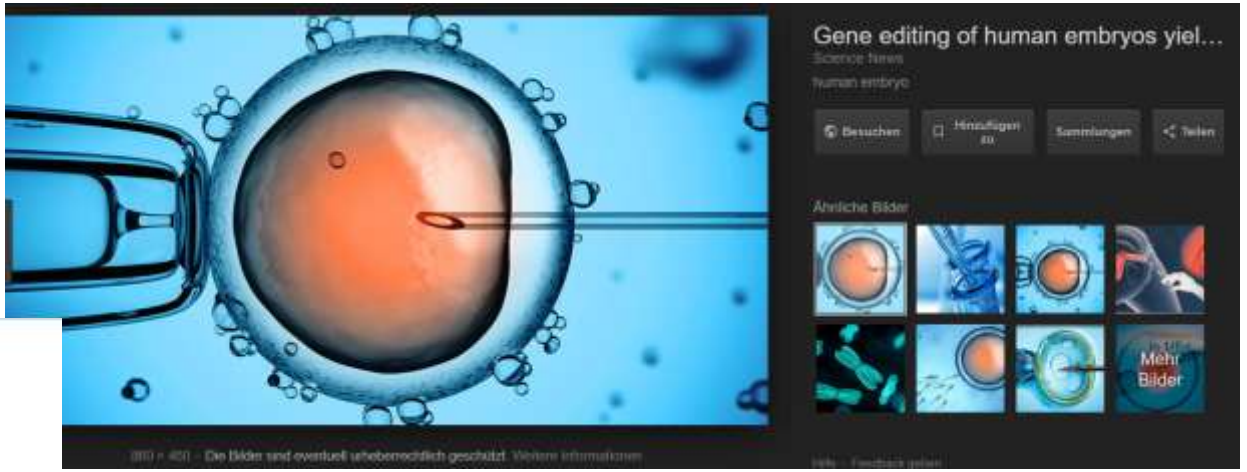
Supporters

Measure co-financed by the European Union

International group of economists, geneticists calls for relaxed crop gene-editing rules to promote food security

Natalie Parletta | Cosmos | April 2, 2019

With renewed attention to implementation and regulation, new plant breeding technologies such as gene editing could make an important contribution to global food security, say a group of plant geneticists and economists.



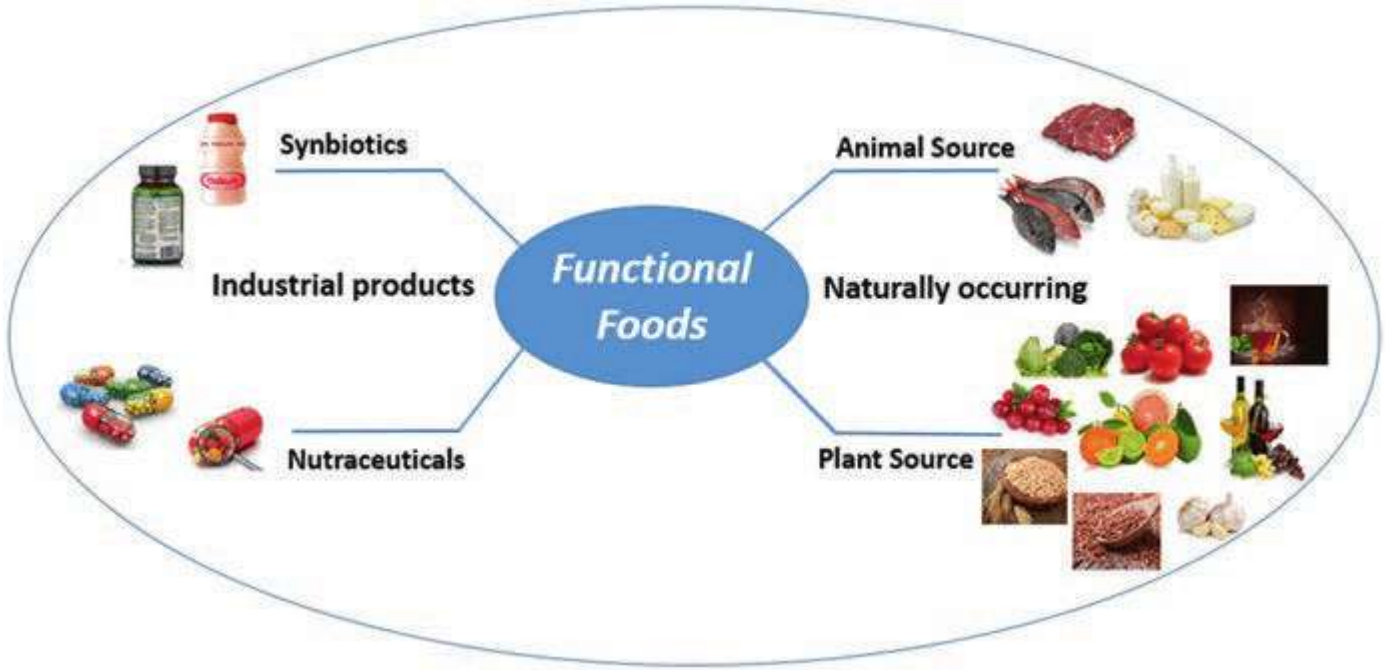
HEALTH

BREAKING: CRISPR Could Be Causing Extensive Mutations And Genetic Damage After All

PETER DOCKRILL 16 JUL 2018

CRISPR has been heralded as one of the most important breakthroughs in modern science, but there could be a hidden and potentially dangerous side effect to the wonders of its genetic editing technology, a new study reveals.

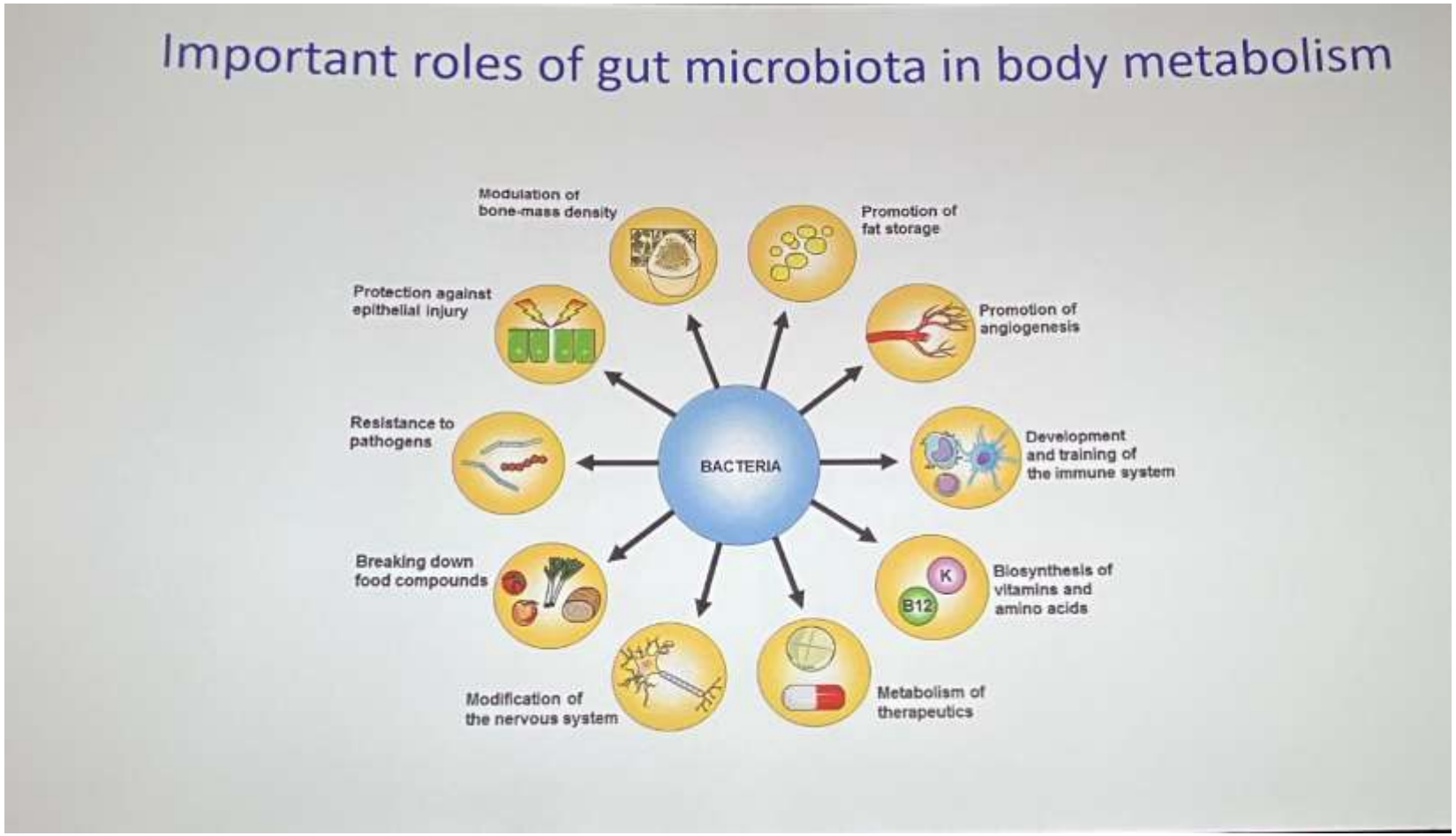
Novel food, functional food, pro-, pre-, syn-, postbiotics



KEYNOTE LECTURE 1

“The role of gut microbiome and its interaction with diet in health and disease”

Prof. Konstantinos Gerasimidis, University of Glasgow, UK.



Ernährung und Mikrobiom sind eng verbunden mit nicht-übertragbaren Erkrankungen.

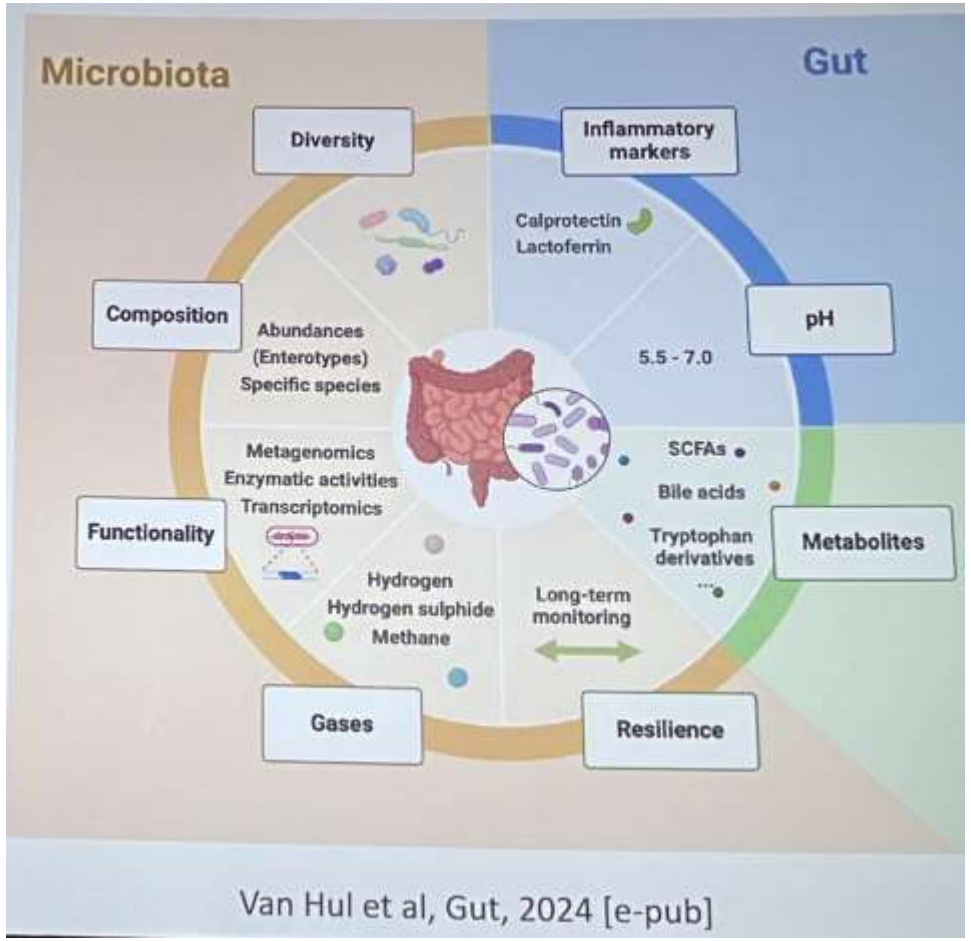
Yakult
Science for Health

KEYNOTE LECTURE 1

“The role of gut microbiome and its interaction with diet in health and disease”

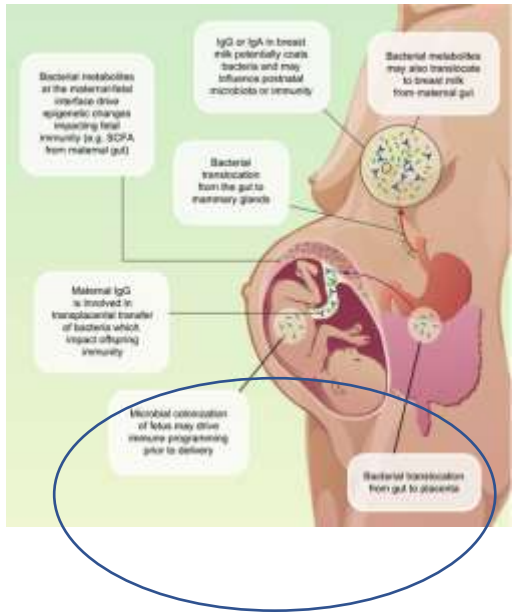
Prof. Konstantinos Gerasimidis, University of Glasgow, UK.

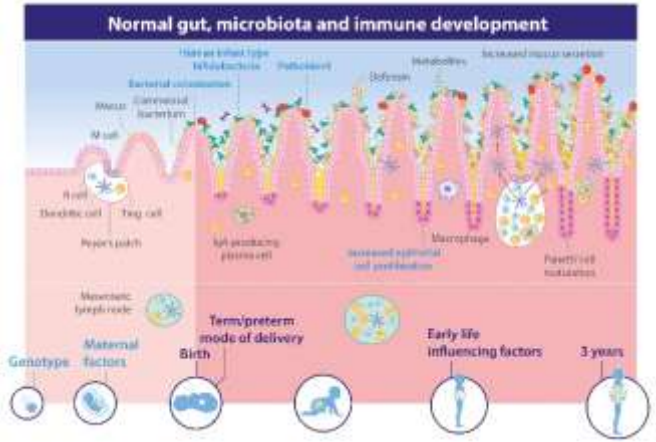
Das Zusammenspiel von Mikrobiota und Darmgesundheit beeinflusst entscheidend wesentliche Vorgänge im Körper.

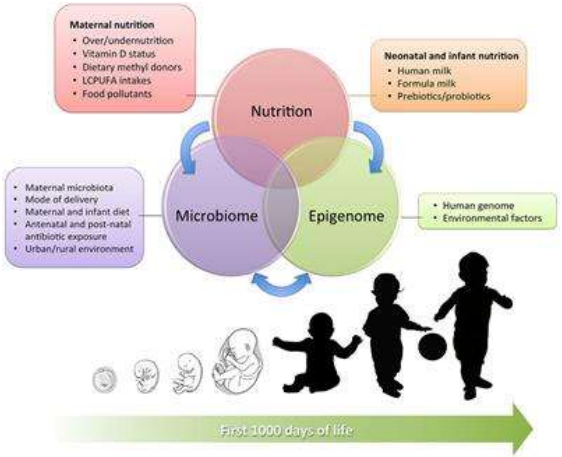


Yakult
Science for Health

Development of microbiota, I.s., and epigenetic system, imprinting

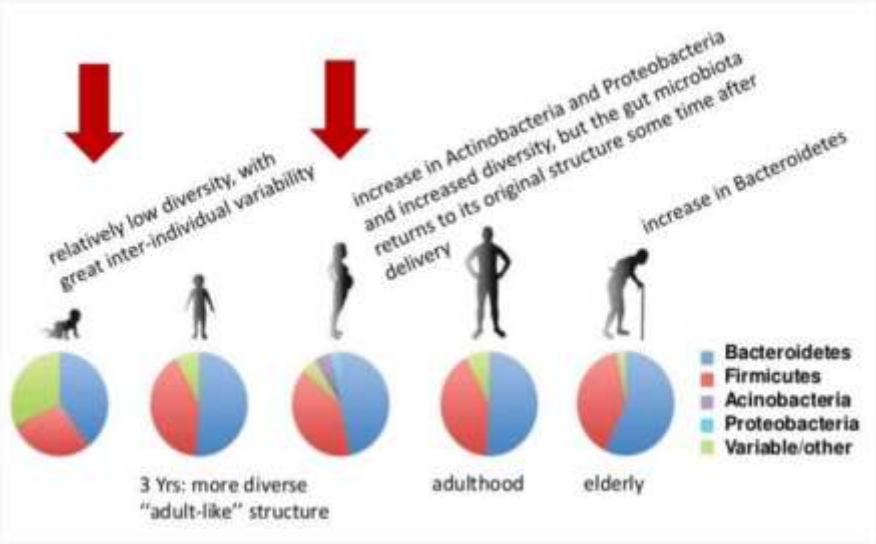






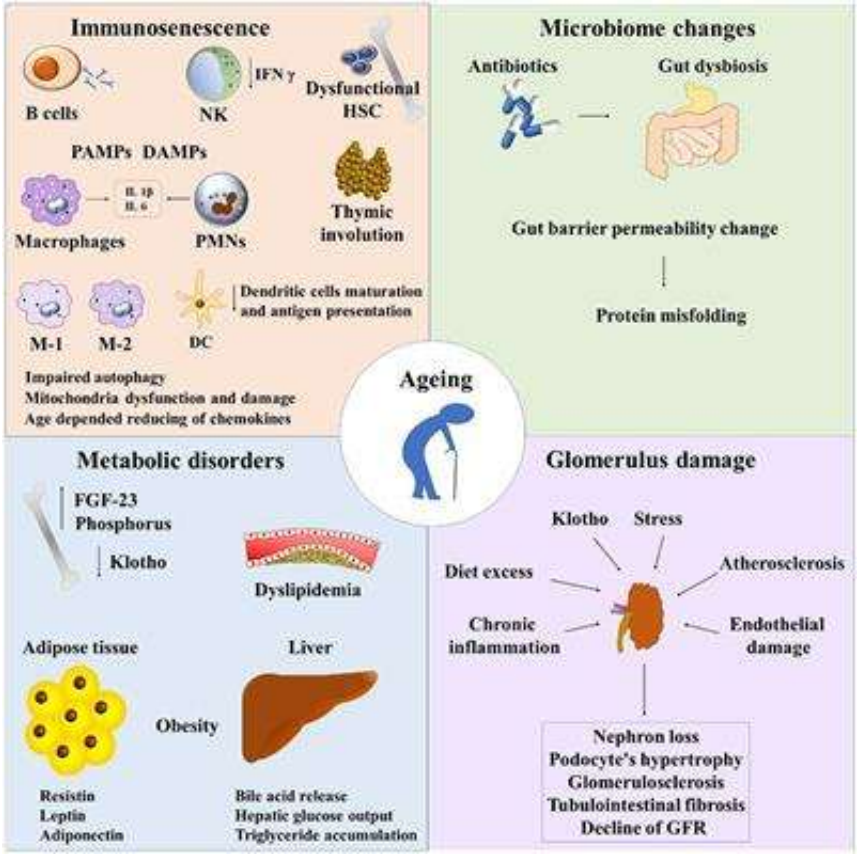
Development prenatal, Interaction with I.S., epigenetic maternal factors ,
Diversity:delivery, breastfeeding, imprinting in 1000 days of life

Interactions Microbiota diversity - I.S.- epigenetic system in senescence



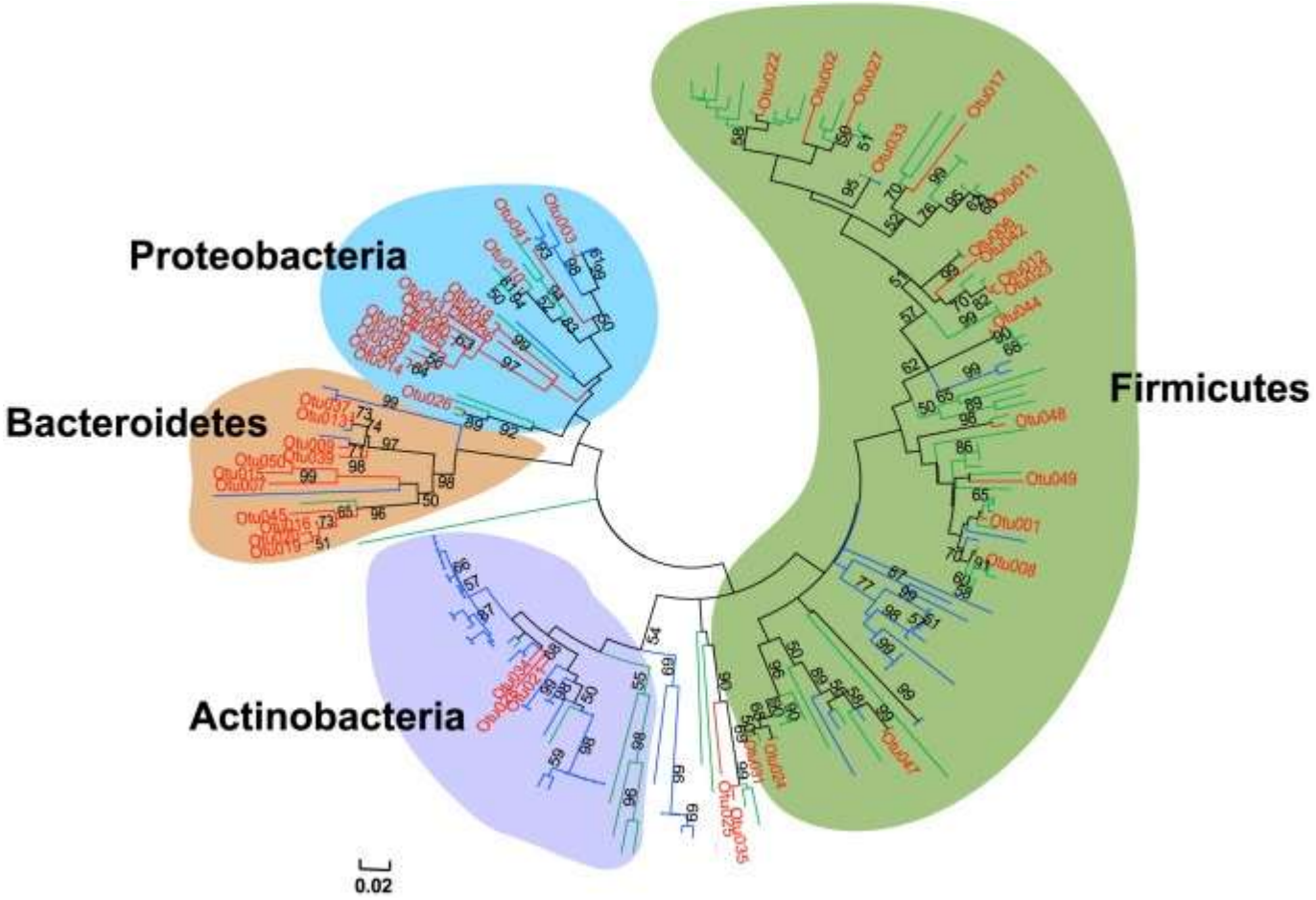
The Impact of the Microbiome on Immunosenescence

Daniel Amsterdam & Barbara E. Ostrov



Inflammaging

Structure microbiota



Microbiome *- a collection of microbial genomes*

Microbiota *– a collection of microbes*

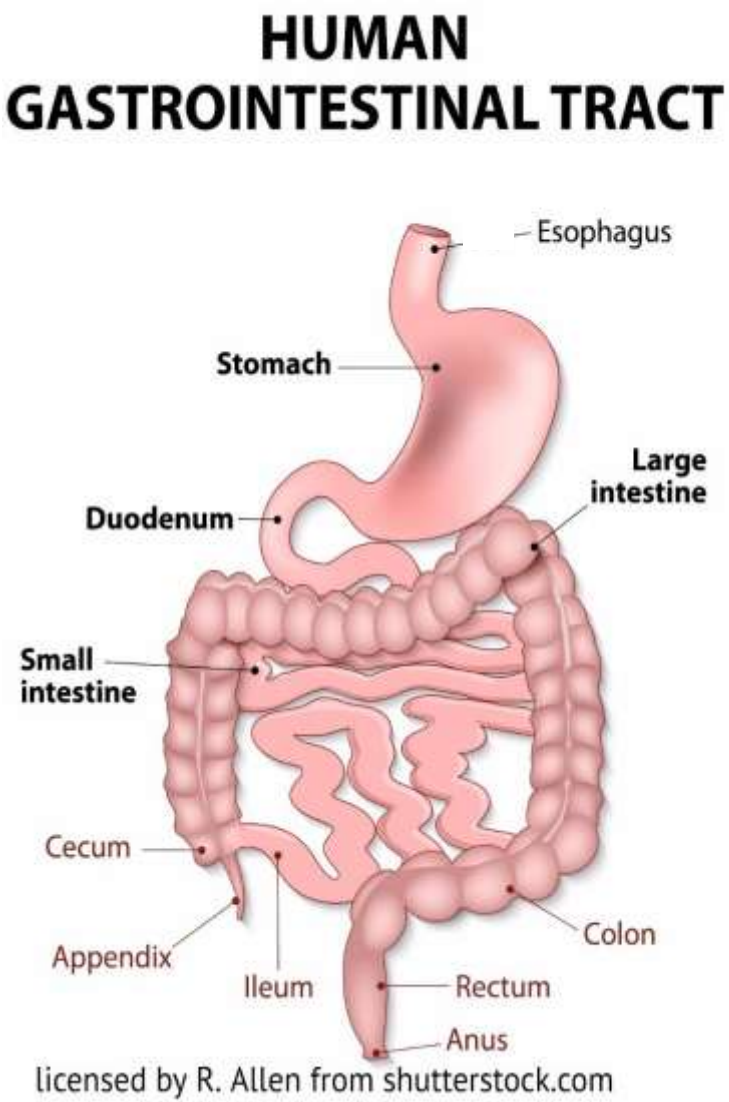
- As many bacteria as host cells in human body

- 150x more bacterial genes than our human genome

GI Microbiota

Stomach & Duodenum
10^1– 10^2 CFU/mL
Helicobacter
Streptococcus

Jejunum & Ileum
10^4 – 10^8 CFU/mL
Bacteroides
Streptococcus
Lactobacillius
Bifidobacteria
Fusobacteria



Colon
10^{10} – 10^{12} CFU/mL
Bacteroides
Prevotella
Facaelbacterium
Ruminococcus
Roseburia
Clostridium
Bifidobacteria
Collinsella
Desulfovibrio
Bilophila
Akkermansia
Methanobrevibacter

"Core" Microbiota

- *Bacteroidetes* (22,9 %)
- *Firmicutes* (64 %)

  *(*32 % of *C. Cluster IV*, 36 % of *C. Cluster XIVa* and 5 % of *Lactobacilli)*

  (Mariat et al., 2009)
- *Actinobacteria* (1- 4 %)
- Verrumicrobiales (1- 4 %)
- Archaeal domain (1- 2,5 %)
- Eukaryotic microorganisms (< 0,1 %)

  (Gerritsen et al., 2011)

Microbiota Functions

- Protective functions
- Structural functions
- Metabolic functions
  - Fermenting dietary fiber into short-chain fatty acids
  - Synthesizing vitamins

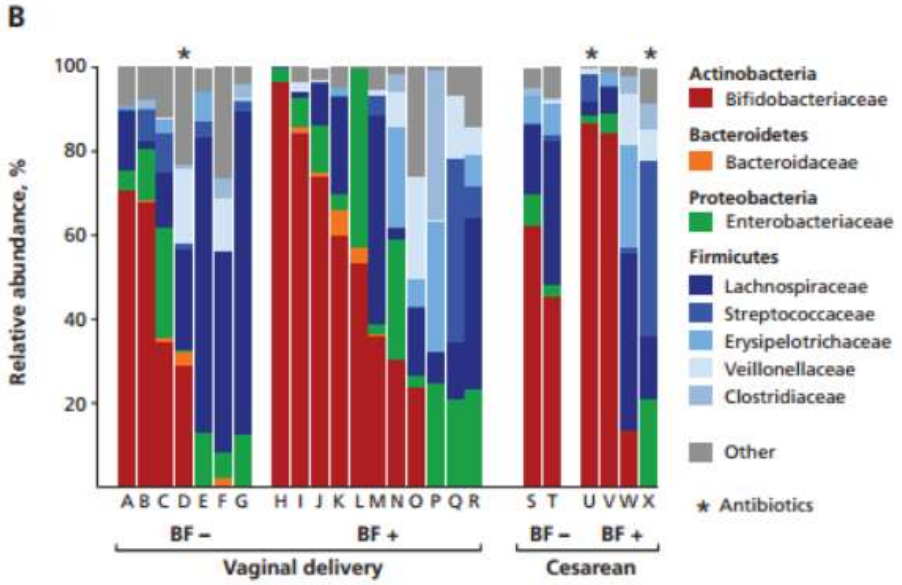
Variation in microbiota structure is high

Despite high variation, GI microbiota depend on :

1. Individuum
2. Area and lifestyle
3. Diet
4. Interventions

Ways of delivery and microbiota: a long lasting difference

Infants born by elective cesarean delivery had particularly low bacterial richness and diversity. formula-fed infants had increased richness of species, with overrepresentation of *Clostridium difficile.*




Research

Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months

CHILD involves more than 10 000 people, including 3 500 infants

GI microbiota: Diversity of groups and functions important for health

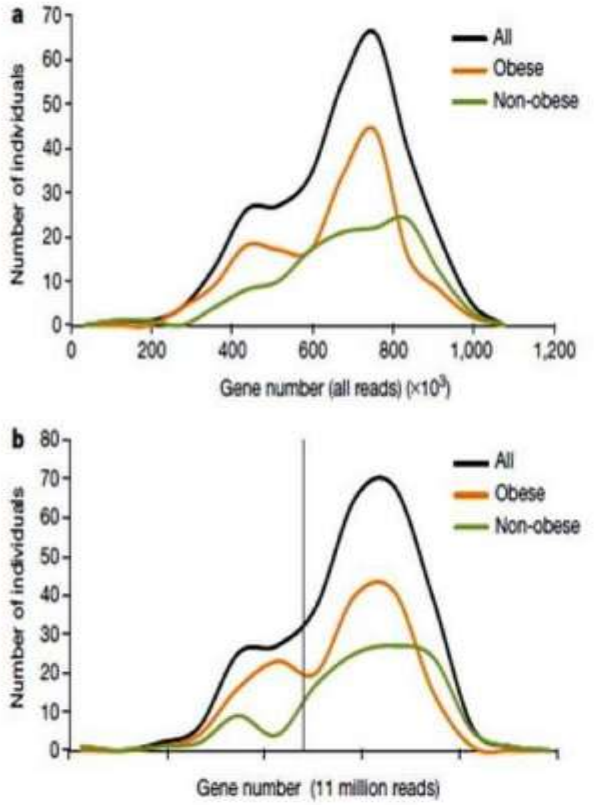
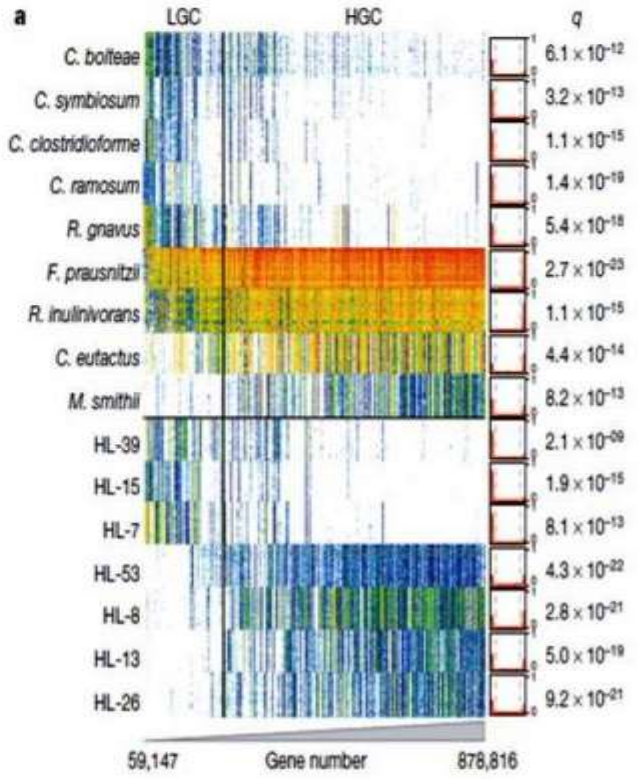
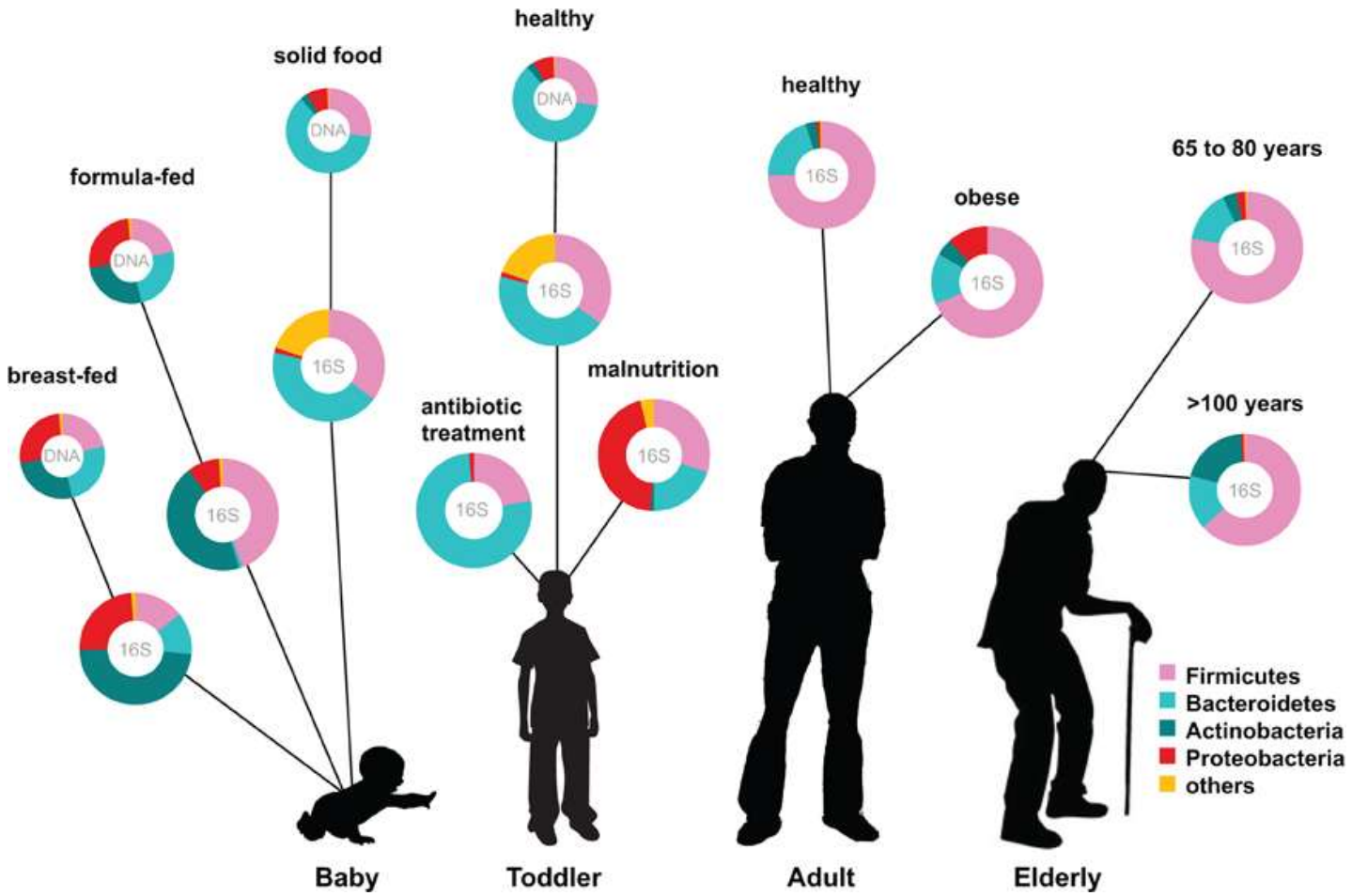


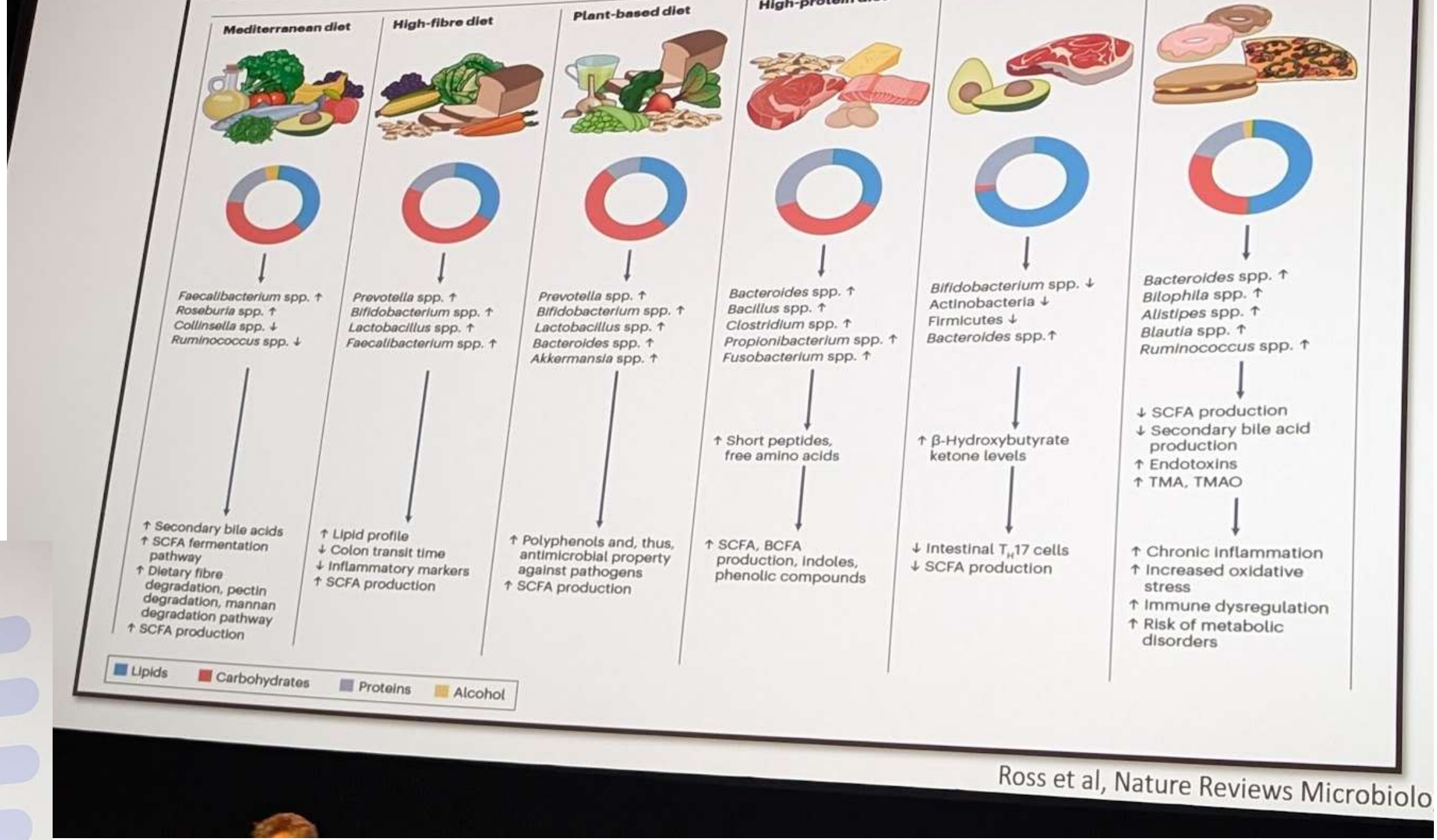
Figure 1 | Distribution of low and high gene count individuals ($n = 292$). a, Gene counts from all uniquely matched reads. b, Gene counts adjusted to 11 million uniquely mapped reads per individual. Vertical line indicates the threshold of the LGC and the HGS individuals; the observed bimodal distribution was not statistically significant by the dip-test.



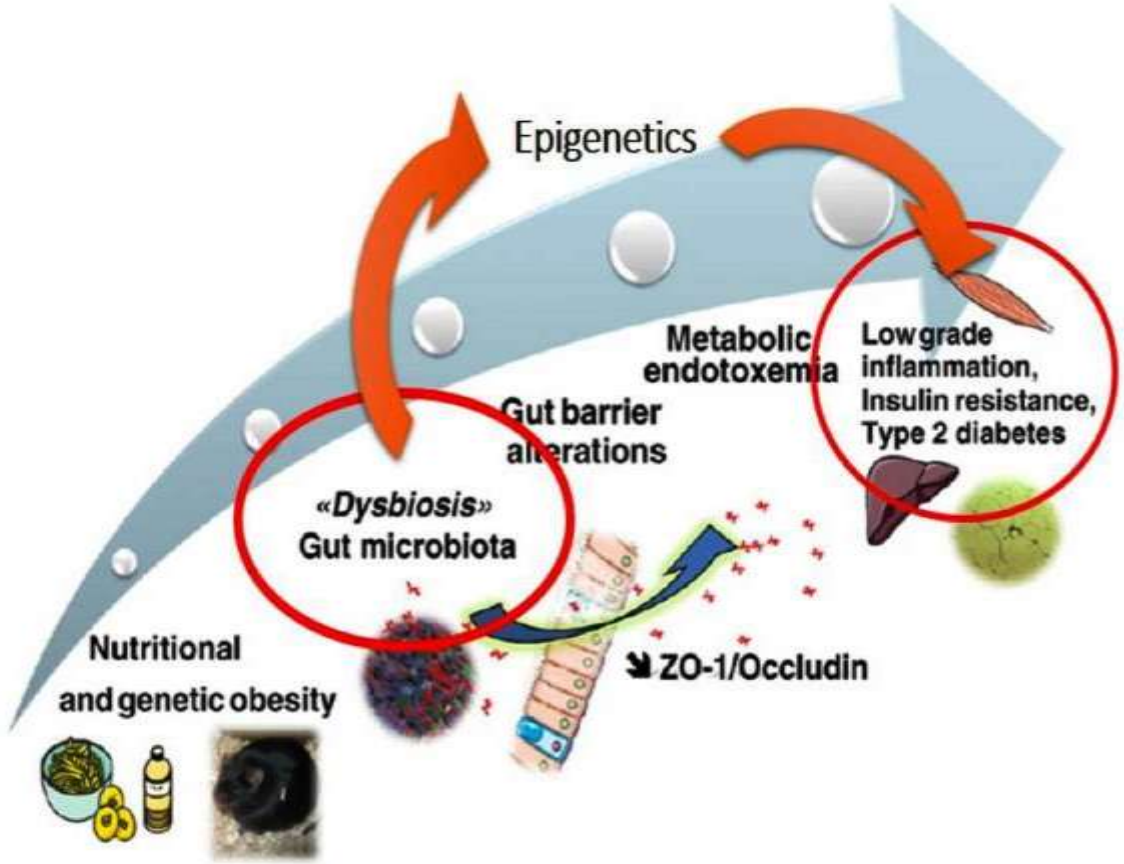
(Le Chatelier E. et al., 2013)
MetaHitConsortium

Aging and Microbiota




Mediterranean diet
High-fibre diet
Plant-based diet
High-protein diet
Faecalibacterium spp. ↑
Roseburia spp. ↑
Collinsella spp. ↓
Ruminococcus spp. ↓
Prevotella spp. ↑
Bifidobacterium spp. ↑
Lactobacillus spp. ↑
Faecalibacterium spp. ↑
Prevotella spp. ↑
Bifidobacterium spp. ↑
Lactobacillus spp. ↑
Bacteroides spp. ↑
Akkermansia spp. ↑
Bacteroides spp. ↑
Bacillus spp. ↑
Clostridium spp. ↑
Propionibacterium spp. ↑
Fusobacterium spp. ↑
Bifidobacterium spp. ↓
Actinobacteria ↓
Firmicutes ↓
Bacteroides spp.↑
Bacteroides spp. ↑
Bilophila spp. ↑
Alistipes spp. ↑
Blautia spp. ↑
Ruminococcus spp. ↑
↑ Secondary bile acids
↑ SCFA fermentation pathway
↑ Dietary fibre degradation, pectin degradation, mannan degradation pathway
↑ SCFA production
↑ Lipid profile
↓ Colon transit time
↓ Inflammatory markers
↑ SCFA production
↑ Polyphenols and, thus, antimicrobial property against pathogens
↑ SCFA production
↑ Short peptides, free amino acids
↑ SCFA, BCFA production, indoles, phenolic compounds
↑ β-Hydroxybutyrate ketone levels
↓ Intestinal T_H17 cells
↓ SCFA production
↓ SCFA production
↓ Secondary bile acid production
↑ Endotoxins
↑ TMA, TMAO
↑ Chronic inflammation
↑ Increased oxidative stress
↑ Immune dysregulation
↑ Risk of metabolic disorders
Lipids
Carbohydrates
Proteins
Alcohol
Ross et al, Nature Reviews Microbiolo

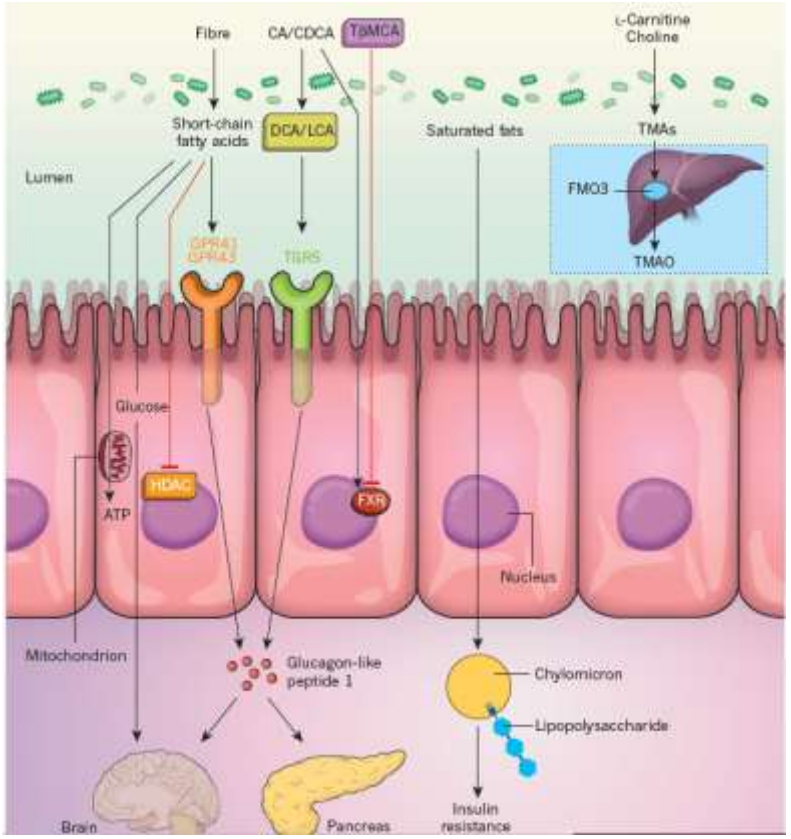
Bacterial cell wall components and Inflammation: dysbiosis, LPS and gut permeability; obesity as a model



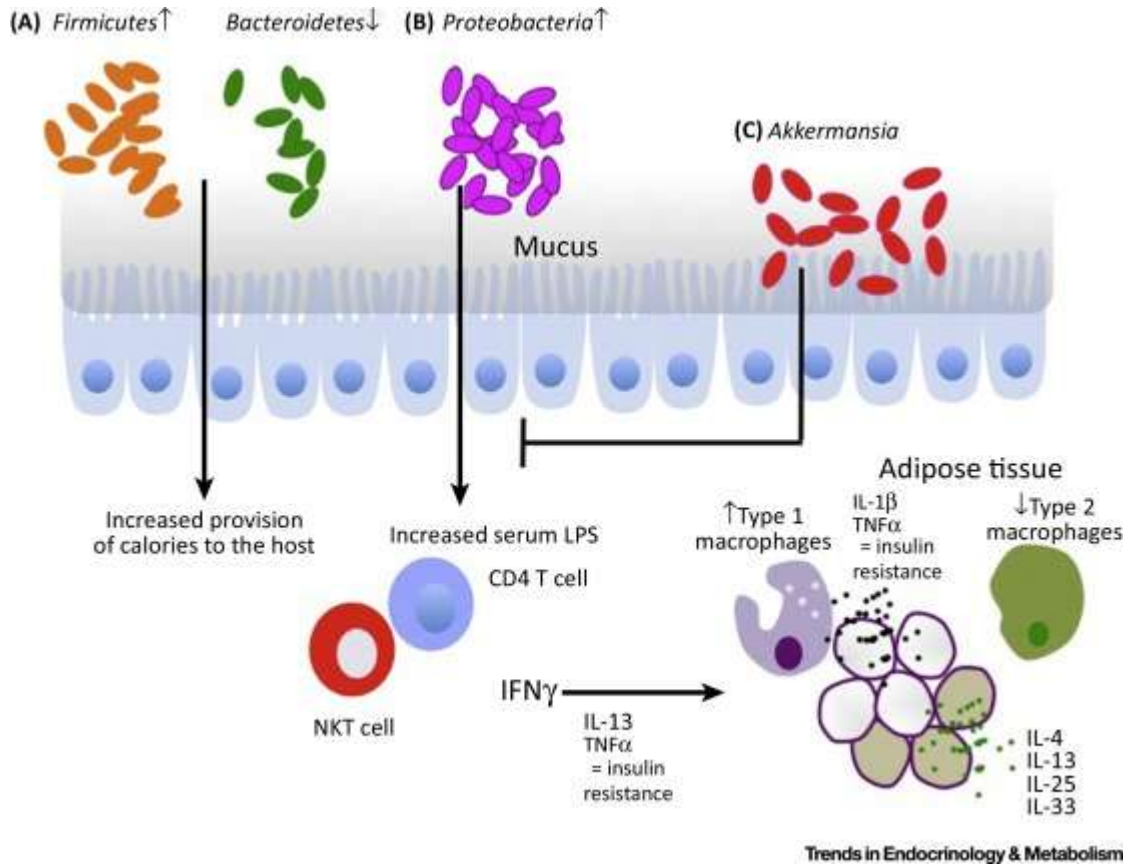
(Cani et al, 2011)

Endotoxins, saturated fats/ chylomicrons trigger inflammation, insulin resistance;
SCFAs may trigger GLP1 activation

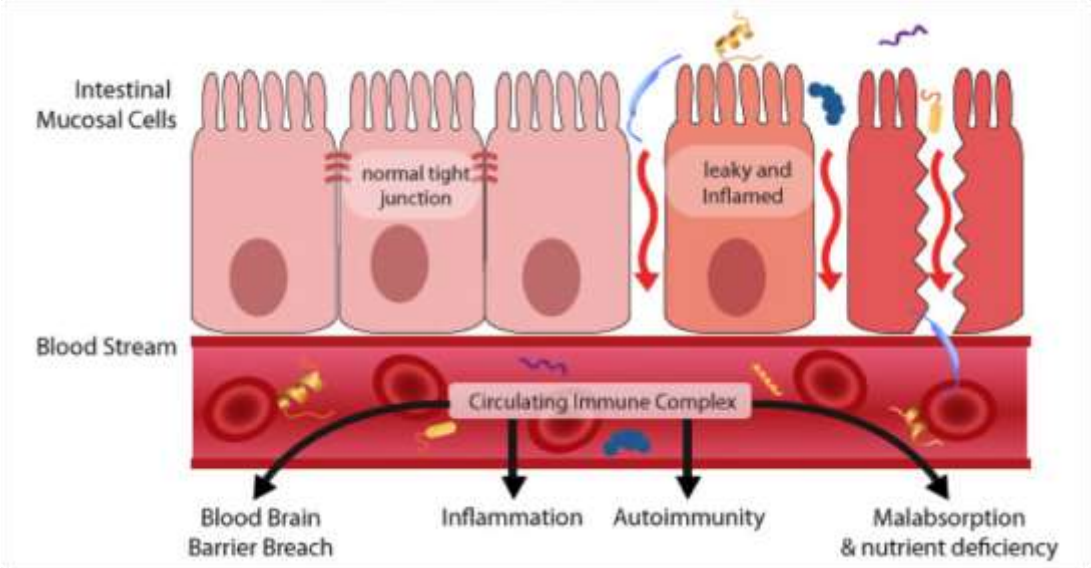
GLP1: incretin improves DMII and obesity

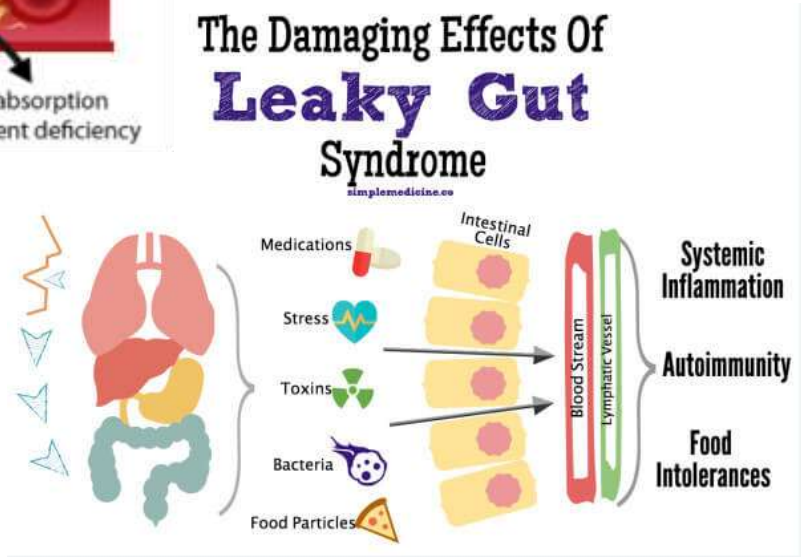


Obesity: Firmicutes: Bacteroidetes; Akkermansia and the cell wall

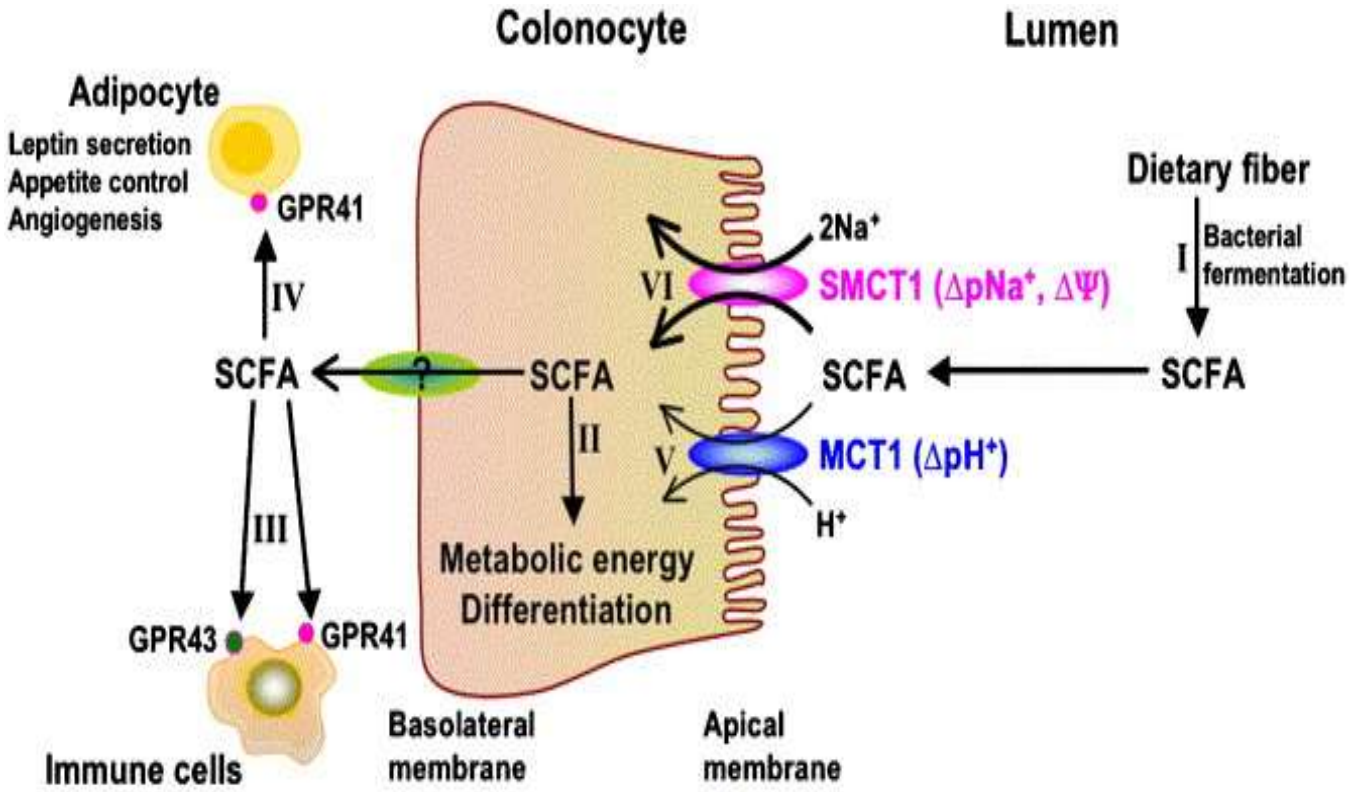


leaky gut: a major health problem





Microbiota metabolites: SCFAs bind to G-Protein-Receptors GPR 41/43 (FFARs)



Anti-inflammatory;

Inhibition of NFκB

(Huster et al., 2013; Flint et al., 2009, Nature Rev)

Microbiota and fermentation products e.g. SCFAs

Clostridial cluster IV (*Rumminococaceae*)	*Clostridial cluster XIVa* (*Lachnospiraceae*)
Faecalibacterium prausnitzii *Butyricoccus* *Clostridium Leptum*	*Eubacterium hallii* *Anaerostipes coli* *Roseburia spp.* *E. rectale spp.*
Resistent starch	*Non starch Polysaccharides*

(Louis and Flint, 2009, FEMS)

Pathways and cross feeding for SCFAs/ Butyrate

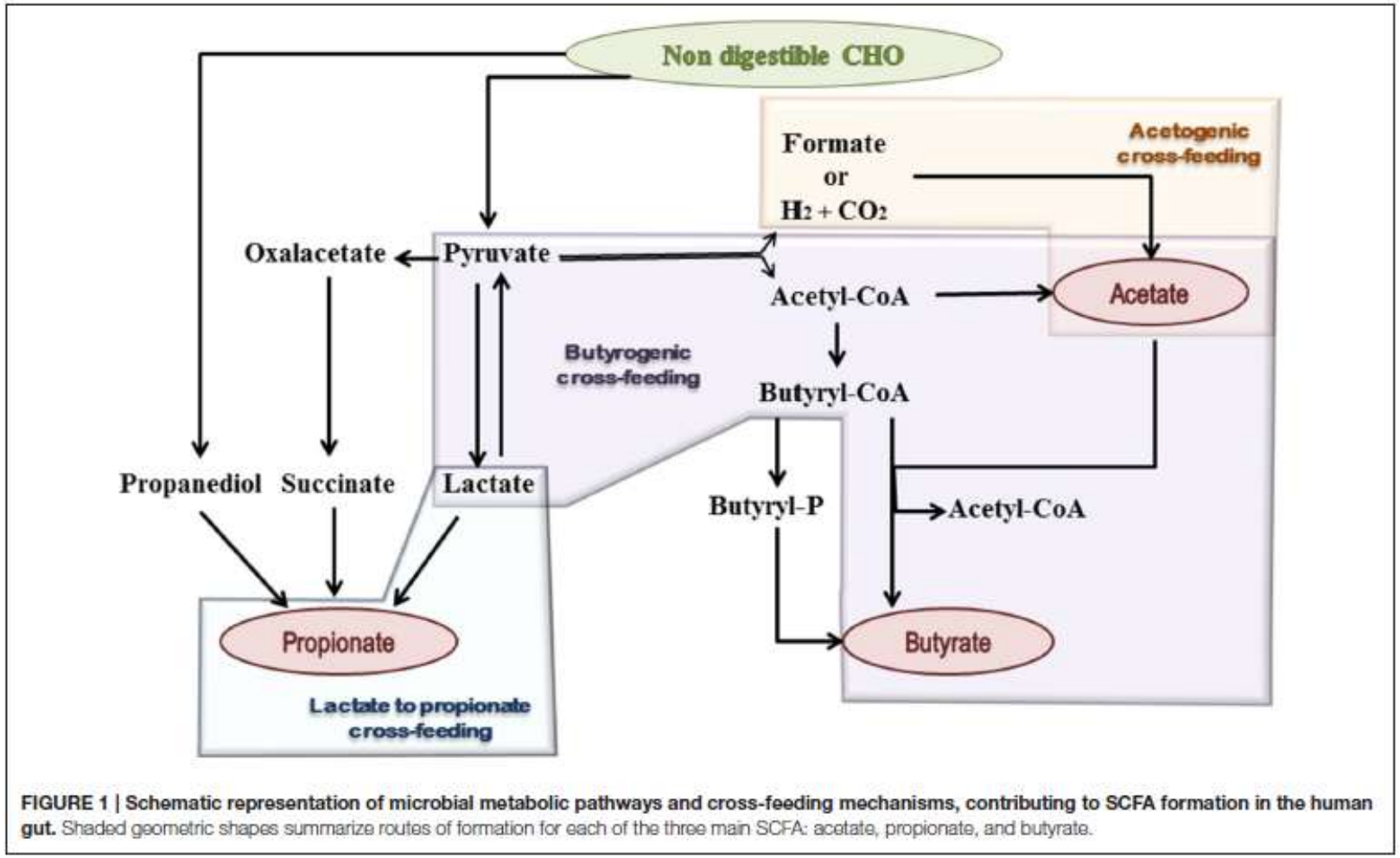
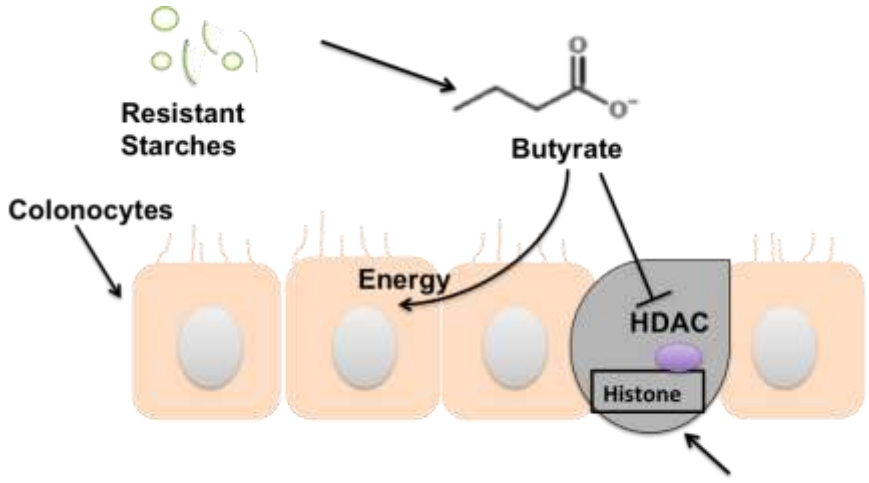


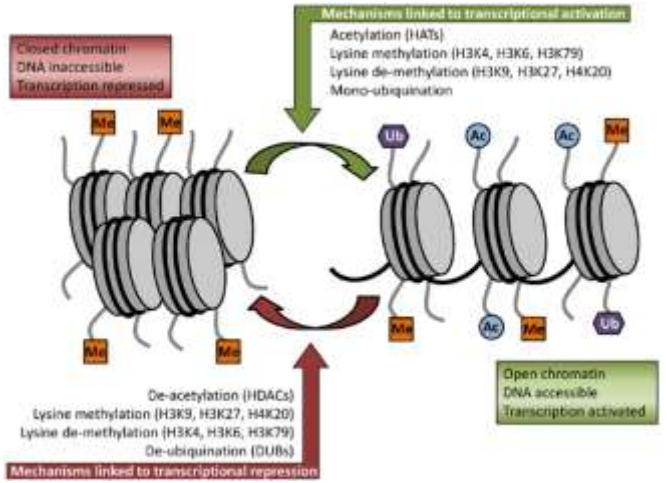
FIGURE 1 | Schematic representation of microbial metabolic pathways and cross-feeding mechanisms, contributing to SCFA formation in the human gut. Shaded geometric shapes summarize routes of formation for each of the three main SCFA: acetate, propionate, and butyrate.

Butyrate and epigenetic histone modulation



Inhibition of Histone Deacetylase Activity by Butyrate[12]

James R. Davie[3]



Butyrate and epigenetics

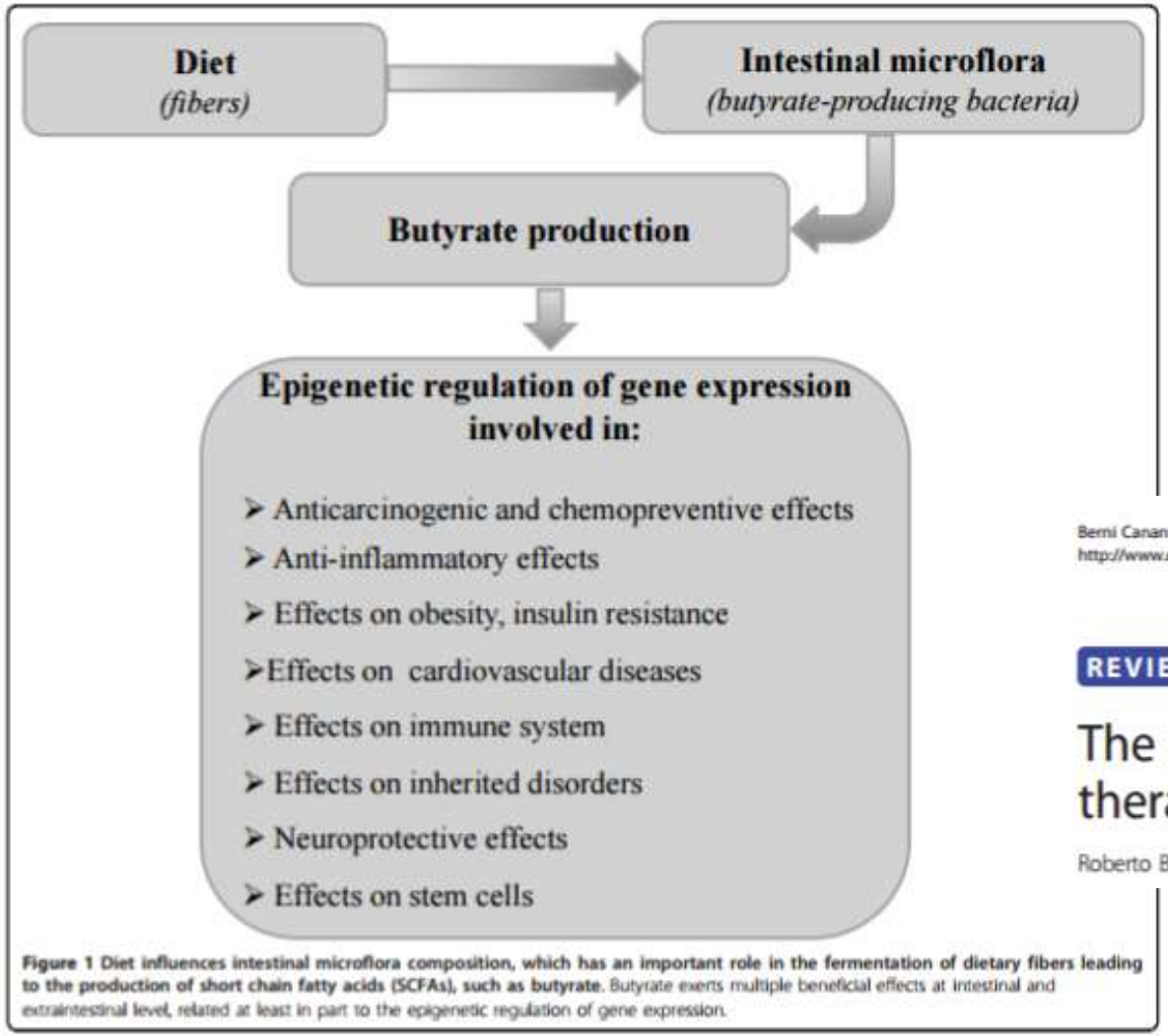


Figure 1 Diet influences intestinal microflora composition, which has an important role in the fermentation of dietary fibers leading to the production of short chain fatty acids (SCFAs), such as butyrate. Butyrate exerts multiple beneficial effects at intestinal and extraintestinal level, related at least in part to the epigenetic regulation of gene expression.

Berni Canani *et al. Clinical Epigenetics* 2012, **4**:4
http://www.clinicalepigeneticsjournal.com/content/4/1/4

CLINICAL EPIGENETICS

REVIEW Open Access

The epigenetic effects of butyrate: potential therapeutic implications for clinical practice

Roberto Berni Canani[1,2*], Margherita Di Costanzo[1] and Ludovica Leone[1]

Butyrate: apoptosis, autophagy, mi- RNAs regulating inflammation, vitro

Table 1. Anti-cancer properties of butyrate through regulating miRNA and gene expression.

TREATMENT	TYPE OF STUDY	METHODS	CANCER CELLS	TARGETS	EFFECT OF BUTYRATE	CITATIONS
NaB	In vitro	PCR	HT-29 (human CRC cells)	MUC2 gene	NaB can inhibit MUC2 gene expression	39
NaB	In vitro	RT-PCR	HCT-116, AW480 (human CRC cells)	Dynamin-related protein 1 (DRP1)	NaB induces apoptosis in CRC	40
NaB, EGCG	In vitro	PCR	HCT-116, RKO, HT-29 (human CRC cells)	P21, P53, NF-kB-p65, HDAC1, DNMT1, survivin	NaB promotes apoptosis and inhibits DNA damage, cell cycle arrest in CRC cells	41
NaB	In vitro	RT-PCR, Western blot assay, MTT proliferation assay	DU145, PC3 cells (human prostate cancer cells)	ANXA1	NaB inhibits proliferation and cell survival in DU145 cells and upregulates ANXA1 expression in prostate cancer	42
Butyrate, TSA	In vitro	Northern blot analyses, H-thymi-dine assay, DNA transfer analysis	HT-29, HT-116 (human CRC cells)	P21 mRNA	Butyrate induces P21 mRNA expression in an immediate early fashion	43
NaB	In vitro	Western blot assay, qRT-PCR	Burkitt lymphoma cell line Raji	c-Myc protein	Butyrate upregulates miR-143, miR-145, and miR-101	44
NaB	In vitro	Western blot analyses, PCR	MDA-MB-231 and MCF7 (human breast cancer cells)		NaB upregulates miR-31	45

Abbreviations: ANXA1, lipocortin 1; DNMT 1, DNA (cytosine-5)-methyltransferase 1; HDACi, histone deacetylase inhibitors; MUC 2, mucin 2; NaB, sodium butyrate; NF-κB, nuclear factor κB; PCR, polymerase chain reaction; qRT-PCR, reverse-transcription quantitative PCR; RT-PCR, real-time PCR; TSA, trichostain A (histone hyperacetylating agent)

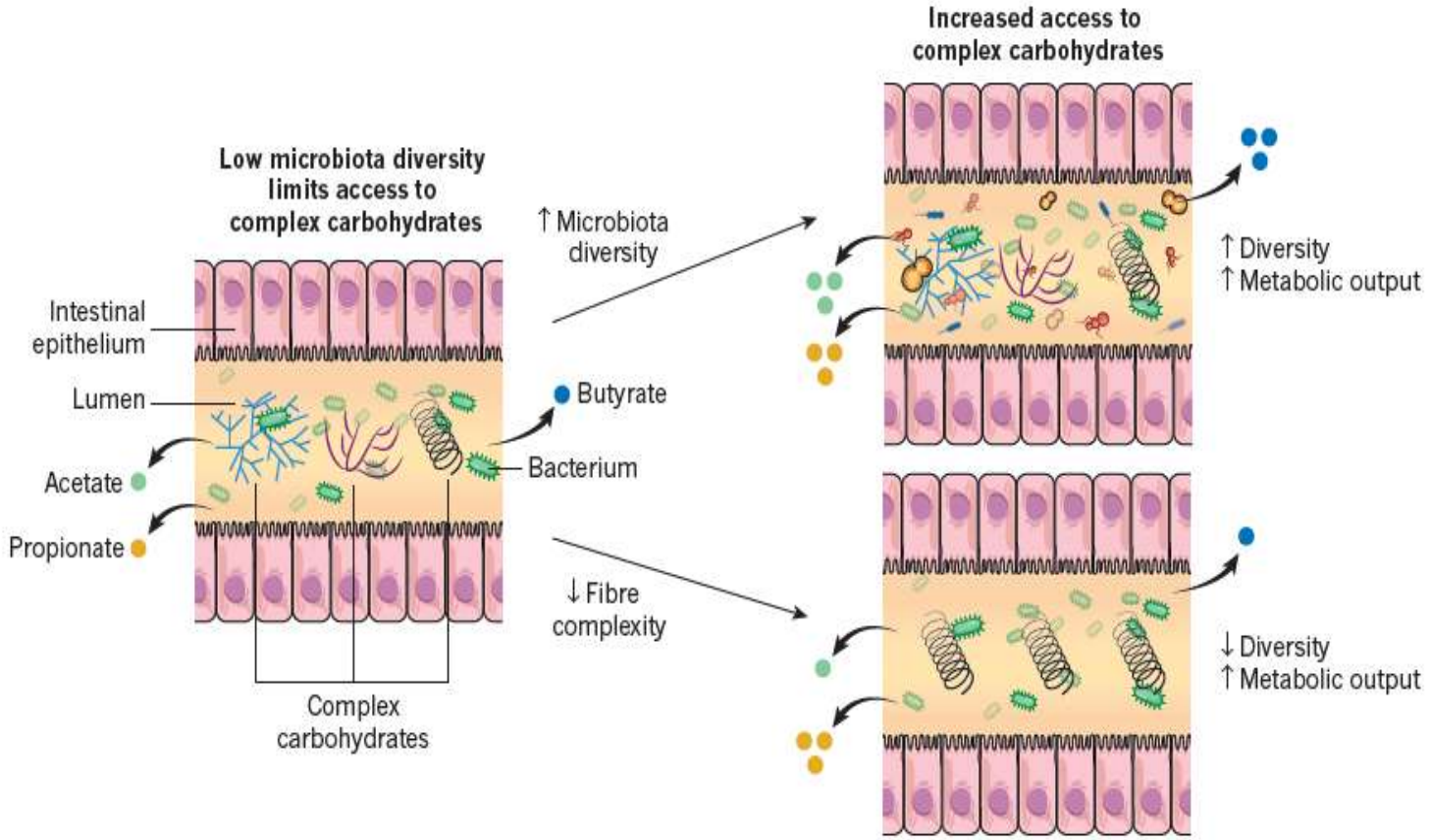
Epigenetic Regulation of Gene Expression Induced by Butyrate in Colorectal Cancer: Involvement of MicroRNA

Karen S Bishop[1], Huawen Xu[2] and Gareth Marlow[3]
[1]Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University

Genetics & Epigenetics
Volume 9: 1–8

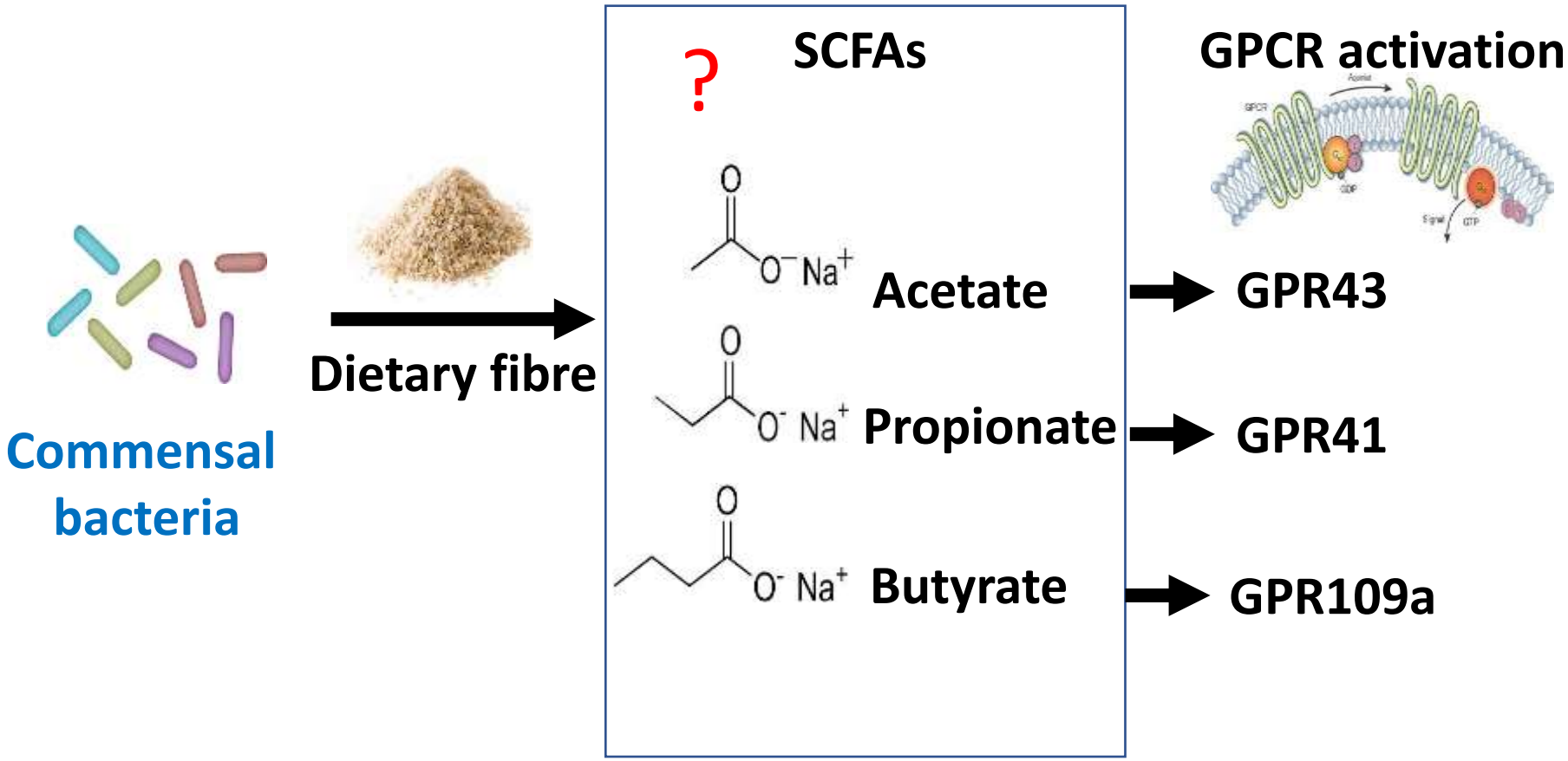
DOI: 10.1177/1179237X17729900
SAGE

Diet dictates the production of SCFAs, diversity of the microbiota, many types of complex carbs

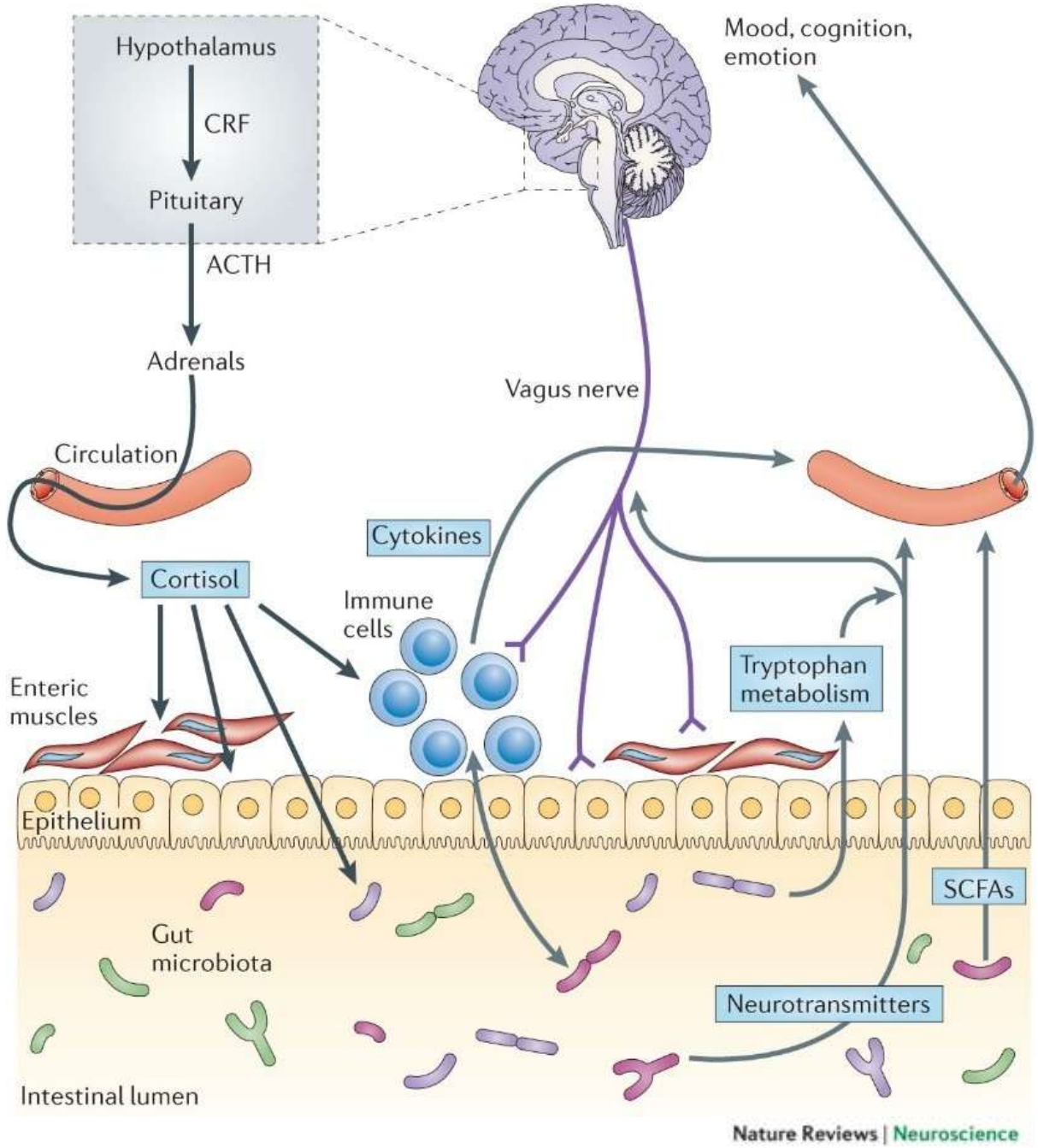


Mechanism of action of fibre: Short-chain fatty acids (SCFAs)?

- SCFAs are major metabolites produced by the microbiota



Gut-Microbiota-Brain Communication

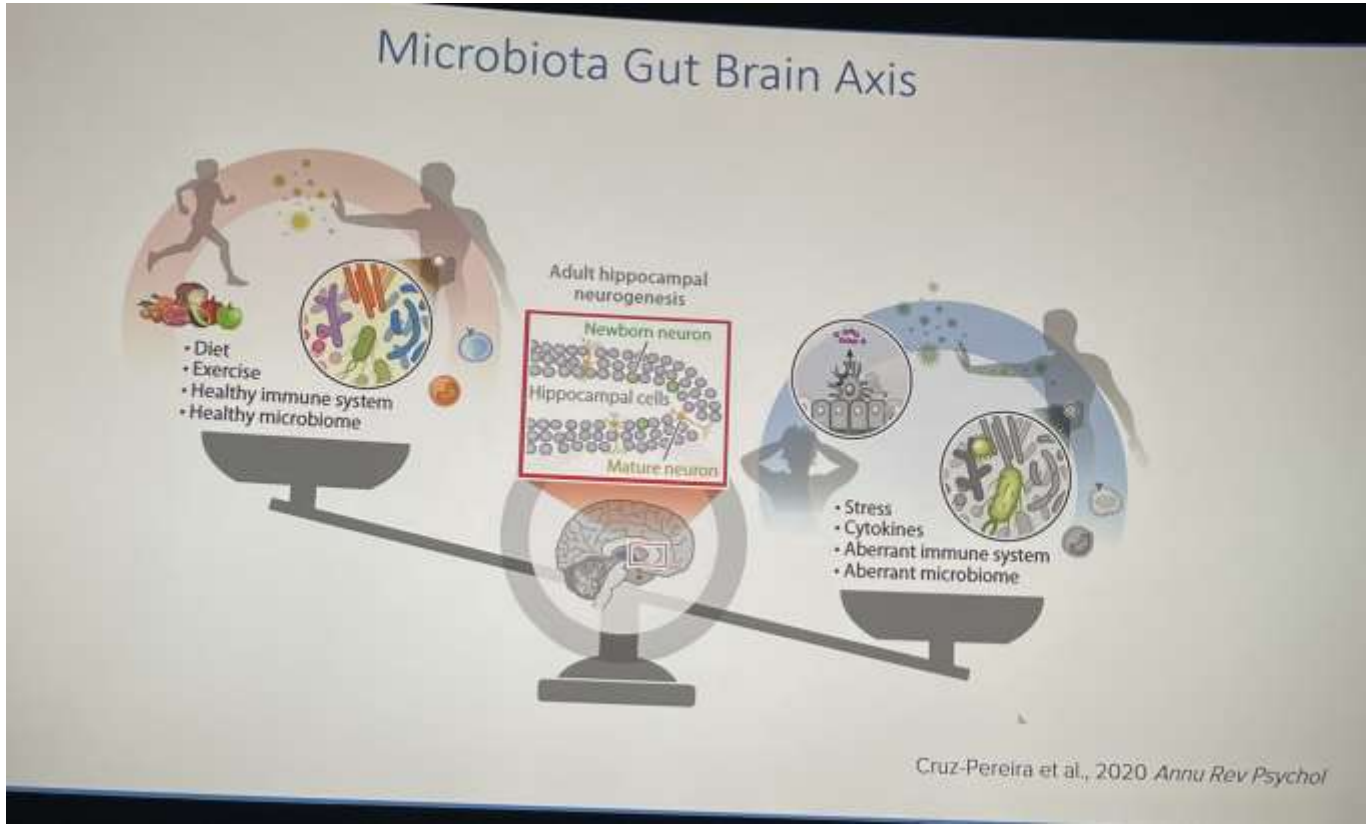


Cryan, John F., and Timothy G. Dinan. "Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour." Nature reviews neuroscience 13.10 (2012): 701-712.

SESSION 3: Mental HEALTH

Lifestyle factors and the gut-brain axis: relevance to Alzheimer's Neurogenese

Prof. Yvonne Nolan, University Cork, Ireland



Mikrobiota mit Einfluss auf die Neurogenese im Hippokampus

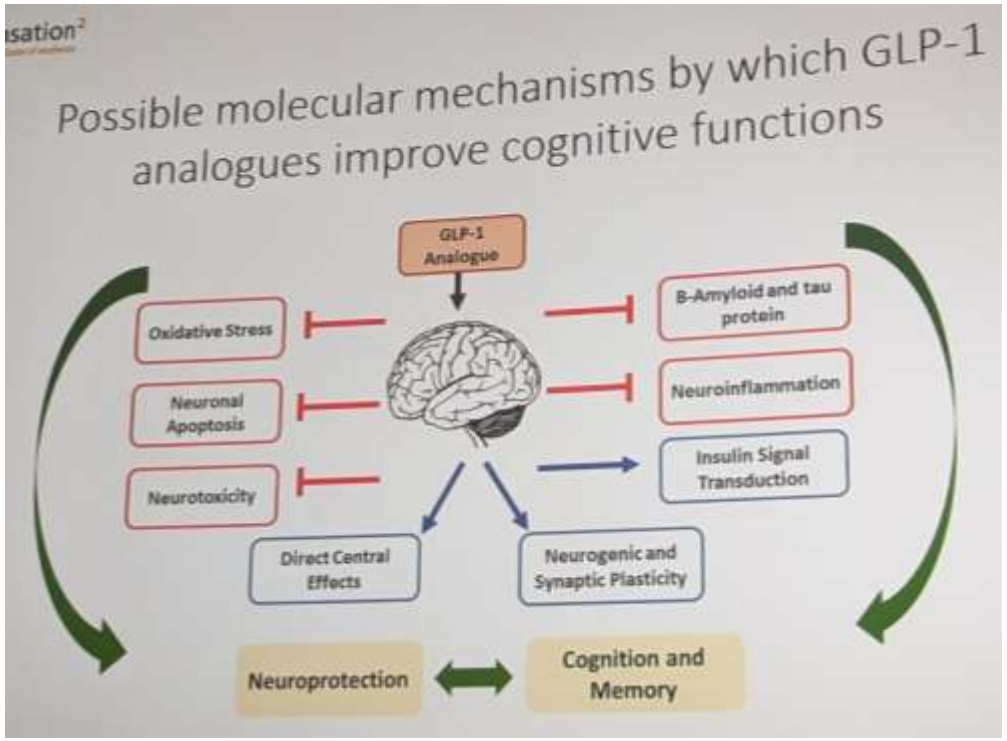
Yakult
Science for Health

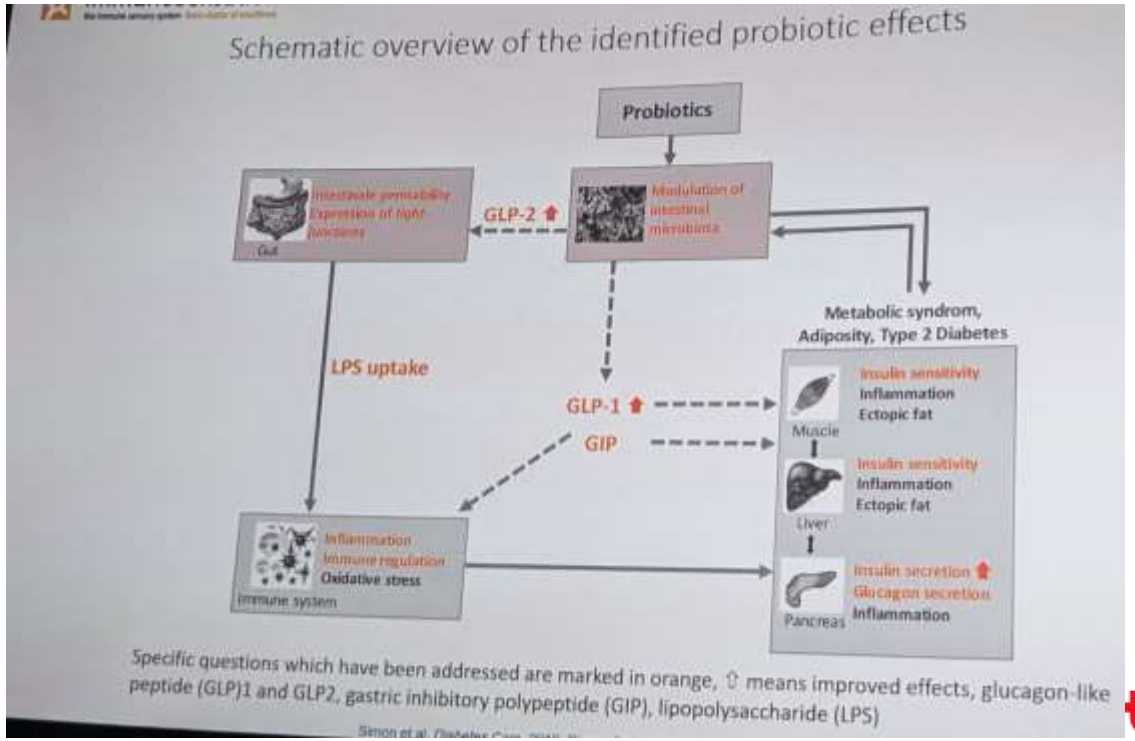
Session 8: Gut Metabolsim

Gut microbiome and its interaction with host metabolic and neurological functionsn Nordic-medit,. Diet

Prof. Marie-Christine Simon, University of Bonn, Germany

GLP1 rezeptor im Rortex, hippocampus, GLP improves cognition, Alzheimer Prophylaxe ?, probiotics stimulate GI micobiota , enhance GLP1



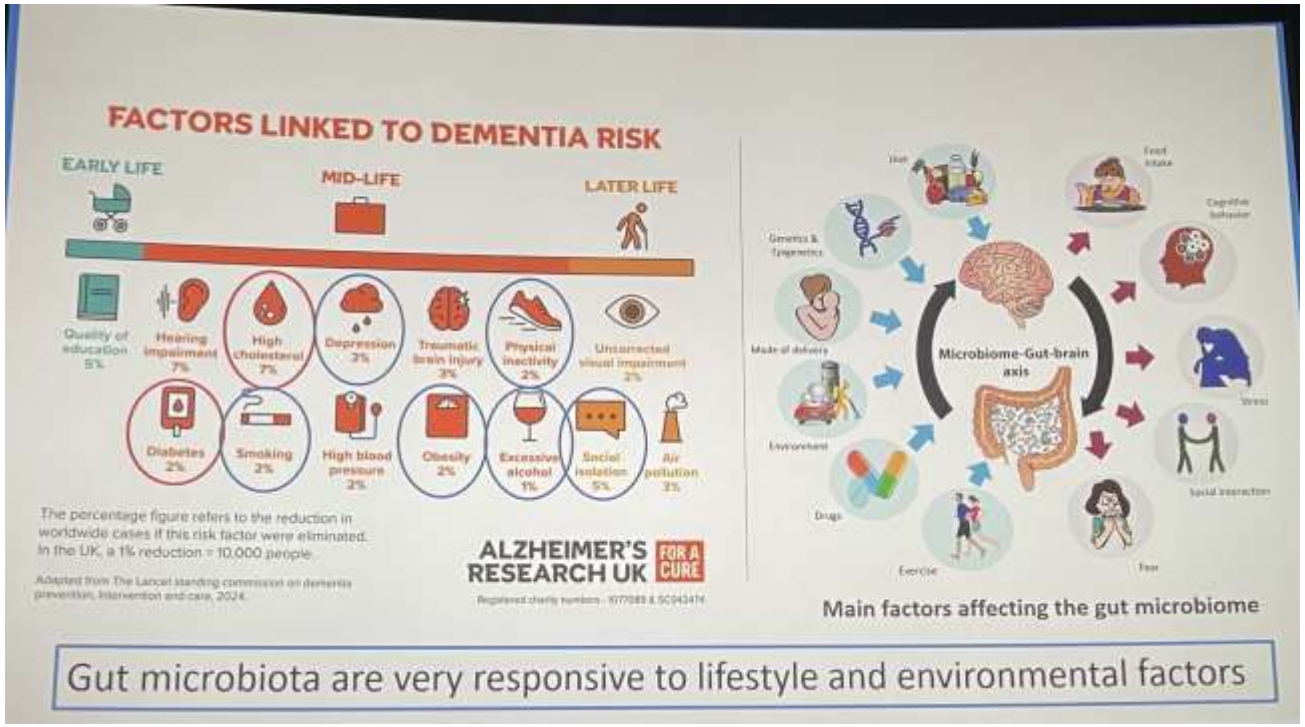


Science for Health

SESSION 3: Mental HEALTH

Lifestyle factors and the gut-brain axis: relevance to Alzheimer's

Prof. Yvonne Nolan, University Cork, Ireland



Lifestyle-Faktoren beeinflussen das Mikrobiom

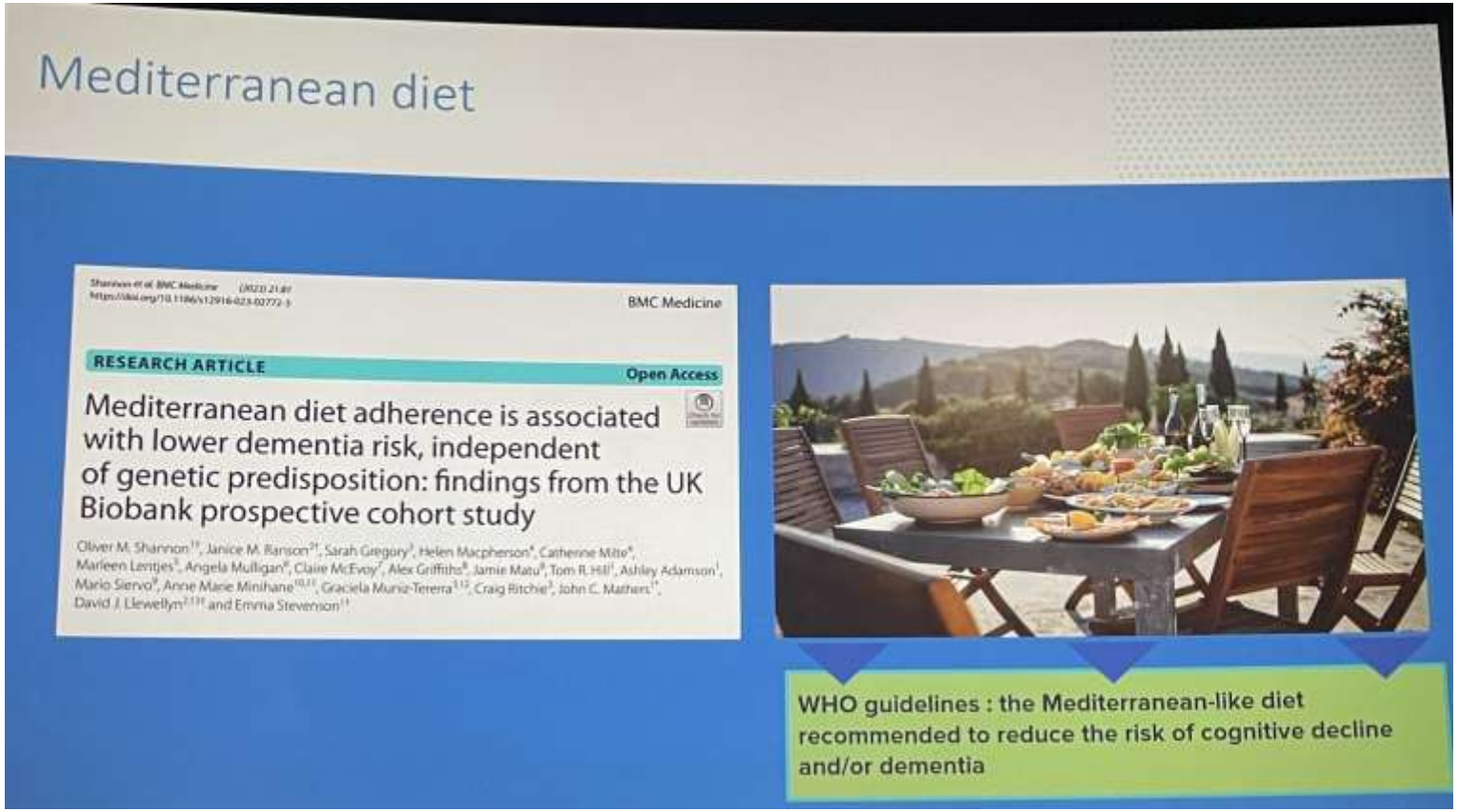
Midlife phase ist wichtig

Yakult
Science for Health

SESSION 3: Mental HEALTH

Lifestyle factors and the gut-brain axis: relevance to Alzheimer's

Prof. Yvonne Nolan, University Cork, Ireland



Positiver Einfluss der mediterranen Ernährung

Yakult
Science for Health

Interventions, examples

Fasting, CR
Probiotika, Prebiotika, Synbiotika, Postbiotika
Epigenetic active foods,
mi RNAs

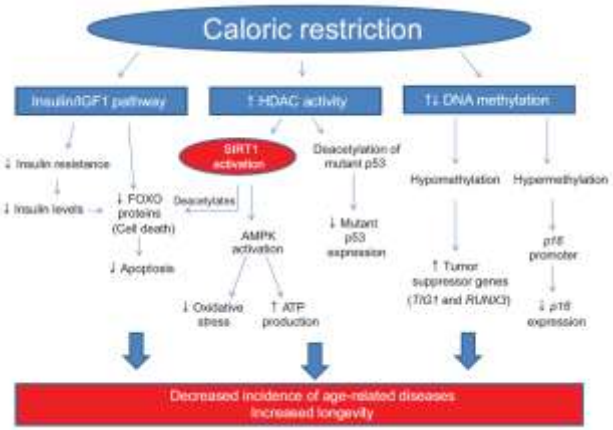
Fasting pathways: Sirt, mTOR pathways

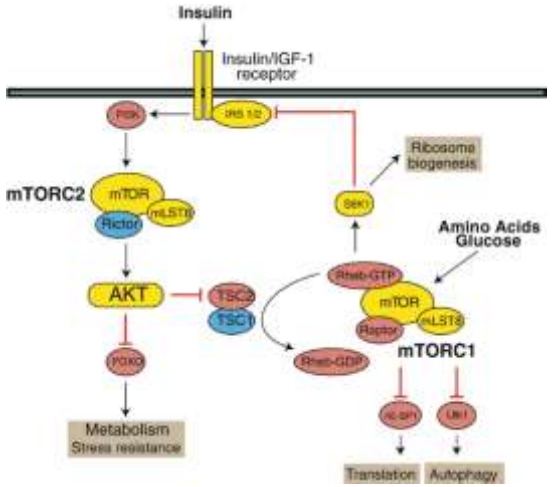
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

LIVER INJURY/REGENERATION

SIRT1 Controls Liver Regeneration by Regulating Bile Acid Metabolism Through Farnesoid X Receptor and Mammalian Target of Rapamycin Signaling

Juan L. García-Rodríguez,[1] Lucía Barbier-Torres,[1] Sara Fernández-Álvarez,[1] Virginia Gutiérrez-de Juan,[1] María J. Monte,[2] Emina Halilbasic,[3] Daniel Herranz,[4] Luis Álvarez,[5] Patricia Aspichueta,[6] Jose J.G. Marin,[2] Michael Trauner,[3] Jose M. Mato,[1] Manuel Serrano,[4] Naiara Beraza,[1,7]* and María Luz Martínez-Chantar[1]*





Caloric restriction and aging change epigenetic CpG -methylation structure

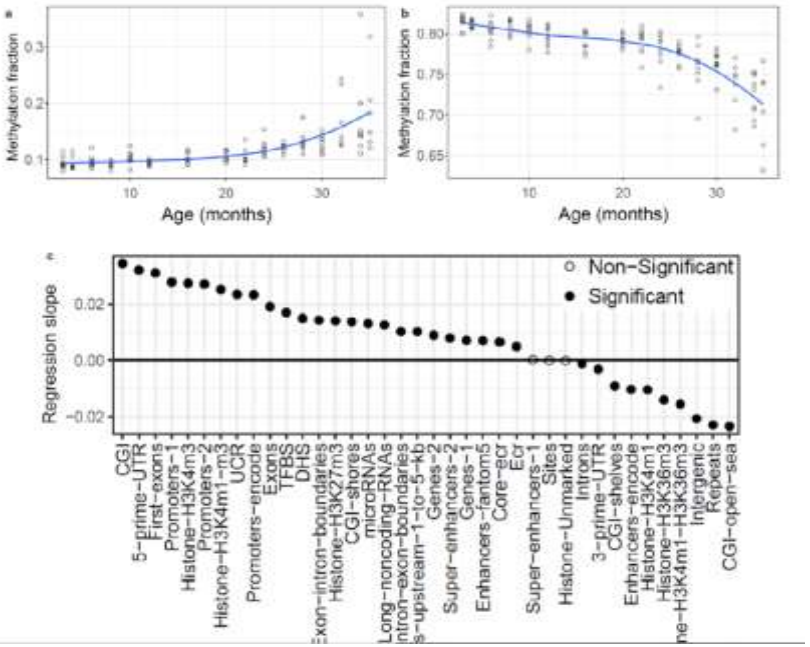
Accepted: 23 January 2018
DOI: 10.1111/acel.12738

ORIGINAL ARTICLE

WILEY Aging Cell

Global remodeling of the mouse DNA methylome during aging and in response to calorie restriction

András Sziráki[1] | Alexander Tyshkovskiy[1,2] | Vadim N. Gladyshev[1]



Fasting and Microbiota

Wien Klin Wochenschr (2015) 127:394–398
DOI 10.1007/s00508-015-0755-1

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Increased gut microbiota diversity and abundance of *Faecalibacterium prausnitzii* and *Akkermansia* after fasting: a pilot study

Marlene Remely · Berit Hippe · Isabella Geretschlaeger · Sonja Stegmayer · Ingrid Hoefinger · Alexander Haslberger

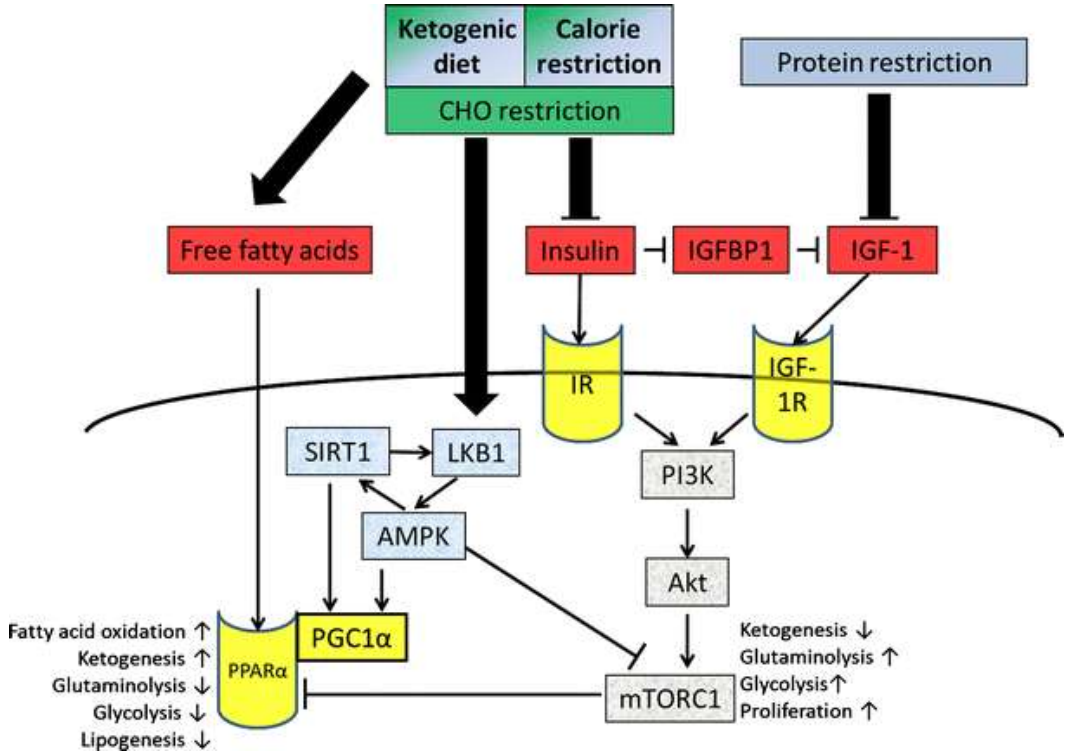
Received: 2 October 2014 / Accepted: 20 January 2015 / Published online: 13 March 2015

Conclusions Our results show that caloric restriction affects gut microbiota by proliferating mucin-degrading microbial subpopulations. An additional intervention with a probiotic formula increased probiotic-administered gut microbial populations.

Why Your Gut Microbes Love Intermittent Fasting

Did you know that most of the cells that make up your body aren't human at all? Some of them are microbial… and when you fast with the LIFE Fasting Tracker app, they fast too.

Caloric restriction, ketogenic diet involve SIRTs (+NAD, clock genes) + mTOR pathways (Metformin). What do fasting mimetics?



Front Psychol. 2015; 6: 27
Published online 2015 Feb 2. doi: 10.3389/fpsyg.2015.00027
PMCID: PMC4313585

Ketosis, ketogenic diet and food intake control: a complex relationship

Antonio Paoli,[1,*] Gerardo Bosco,[1] Enrico M. Camporesi,[2,3] and Devanand Mangar[3,4]

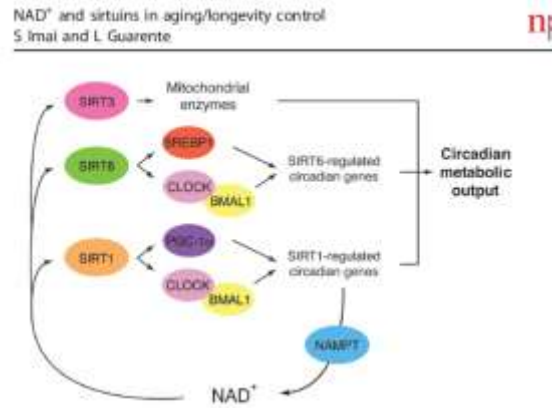


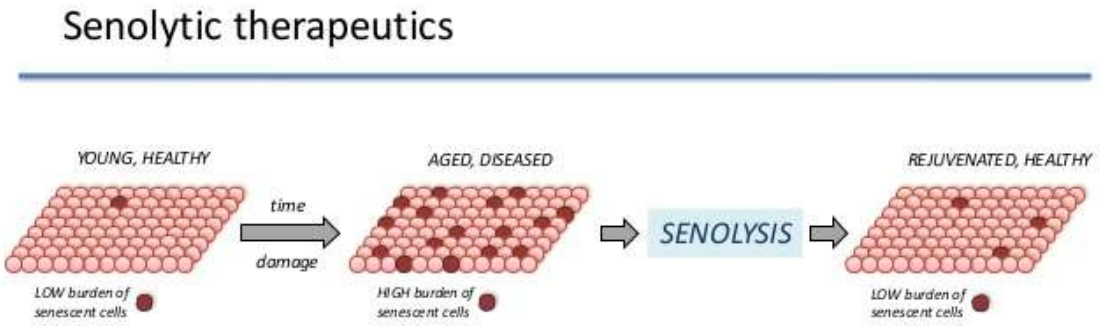
Figure 3. Circadian regulation of NAD+ biosynthesis and metabolism by NAMPT and sirtuins. *Nampt* is one of the SIRT1/CLOCK/BMAL1-regulated circadian genes, and SIRT1 and NAMPT comprise a novel circadian regulatory feedback loop, producing the circadian oscillation of NAD+. This circadian oscillation of NAD+ drives SIRT1, SIRT3, and SIRT6 activities. SIRT1 feedbacks the key circadian transcription factors CLOCK/BMAL and regulates genes related to peptide and cofactor biosynthesis in the liver. SIRT1 also regulates *Bmal1* expression through PGC-1α in the suprachiasmatic nucleus. SIRT6 controls the chromatin recruitment of CLOCK/BMAL1 and SREBP1 and regulates genes related to lipid and carbohydrate metabolism. SIRT3 regulates oxidative metabolism in mitochondria through circadian deacetylation of mitochondrial oxidative enzymes. All these circadian activity changes of sirtuins produce robust metabolic outputs in many different tissues and organs. NAD+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase.

npj | Aging and Mechanisms of Disease
REVIEW ARTICLE OPEN

It takes two to tango: NAD+ and sirtuins in aging/longevity control

Shin-ichiro Imai[1] and Leonard Guarente[2,*]

Caloric restriction: Rejuvenetion by senolysis? role for autophagy ?



Is fasting senolytic? | Josh Mitteldorf
https://joshmitteldorf.scienceblog.com/2017/.../i

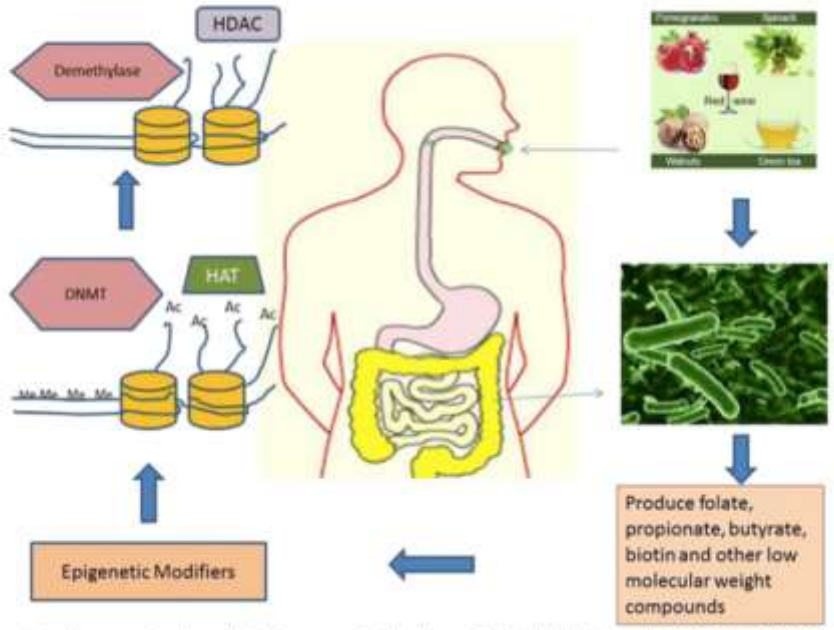
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0092-9

Senolytics improve physical function and increase lifespan in old age

Ming Xu[1,2*], Tamar Pirtskhalava[1], Joshua N. Farr[1], Bettina M. Weigand[1,3], Allyson K. Palmer[1],

83rd ICREA Colloquium, 2018

Effect of Plant Ingredient and Diet on Microbiota and Metabolites



Influences of diet and the gut microbiome on epigentic modulation in cancer and other diseases, Paul et al.; clinical epigentics 2015 7:112; DOI 10.1186/s13148-015-0144-7

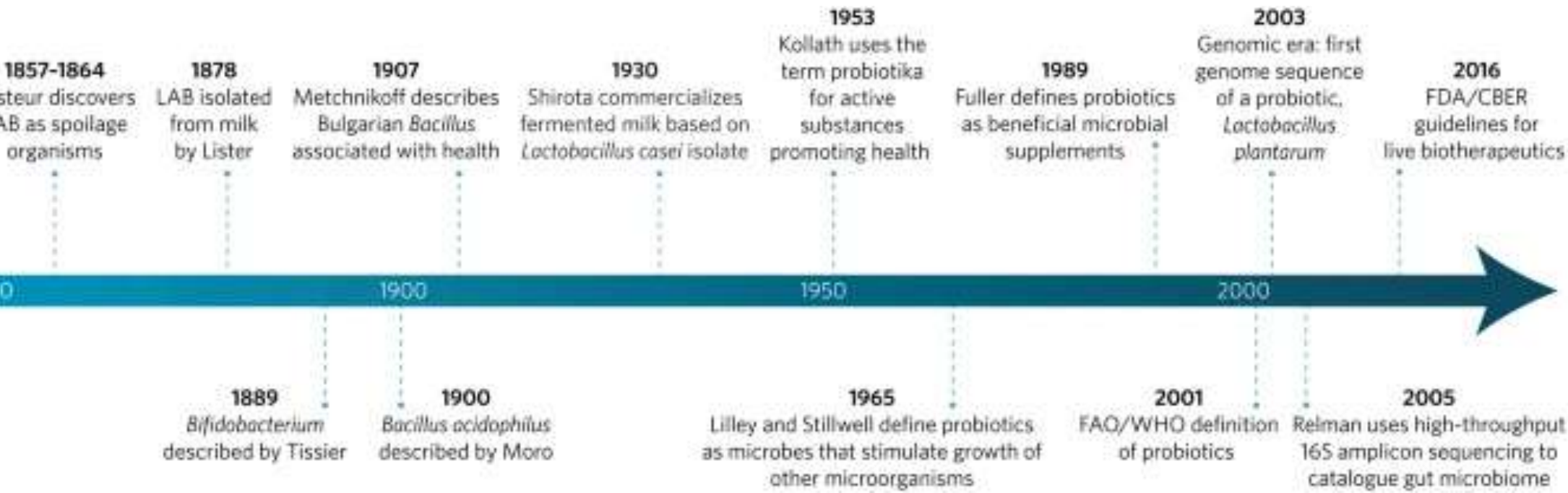
Ingredients Shot

STOFF	WIRKSTOFF	MENGE / 25ML	Wirkstoff
Blueberry Extract	Anthocyanins/ Anthocyanidin..	40 mg	14mg 10mg
Broccoli Extract	Sulpharapane, Glucoraphin..	30 mg	
Apfel extract	Phlorentin, Quercetin..	50 mg	
Citrus extract	Naringin..	40 mg	
Nikotinamid	Nikotinamid ribosid	24 mg	
Zinkgluconat	Zink	7.5 mg	

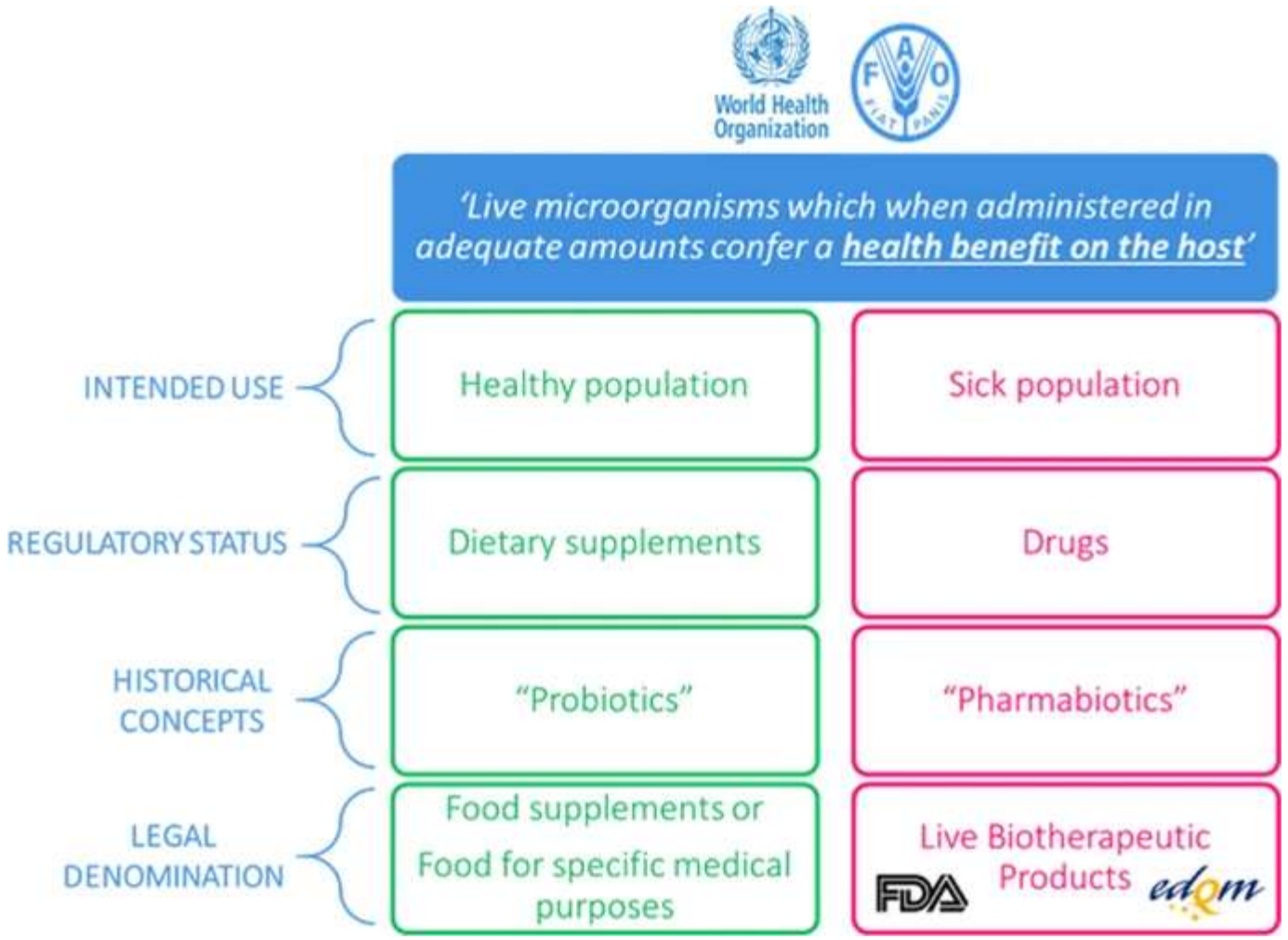
Wasser, Stevia, Erythrit

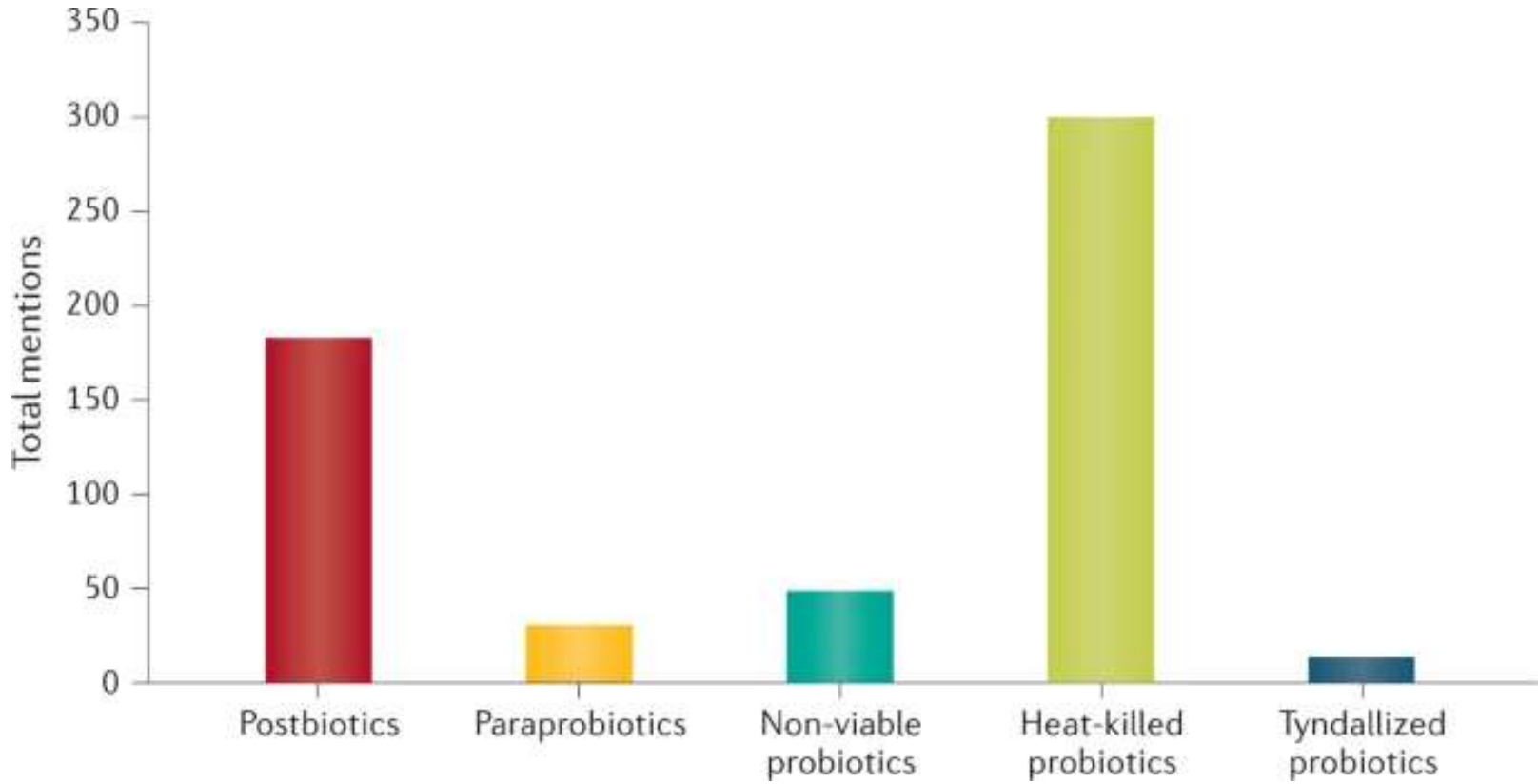
Probiotic

- Positive effects on health already 100 years ago suggested by Nobel Prize winner Elie Metchnikoff [Metchnikoff, 2004]
- Definition: “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [FAO/WHO, 2002]
- Over 8000 research articles published since 2002 → several probiotic products on the market [Hill et al., 2014]
- Cell components of probiotics able to induce effects in host [Dotan and Rachmilewitz, 2005] but requirement for survivable cells remains a crucial factor for efficacy [Ma et al., 2004]


1857–1864
steur discovers
AB as spoilage
organisms
1878
LAB isolated
from milk
by Lister
1907
Metchnikoff describes
Bulgarian Bacillus
associated with health
1930
Shirota commercializes
fermented milk based on
Lactobacillus casei isolate
1953
Kollath uses the
term probiotika
for active
substances
promoting health
1989
Fuller defines probiotics
as beneficial microbial
supplements
2003
Genomic era: first
genome sequence
of a probiotic,
Lactobacillus
plantarum
2016
FDA/CBER
guidelines for
live biotherapeutics
0
1900
1950
2000
1889
Bifidobacterium
described by Tissier
1900
Bacillus acidophilus
described by Moro
1965
Lilley and Stillwell define probiotics
as microbes that stimulate growth of
other microorganisms
2001
FAO/WHO definition
of probiotics
2005
Relman uses high-throughput
16S amplicon sequencing to
catalogue gut microbiome

Definitions



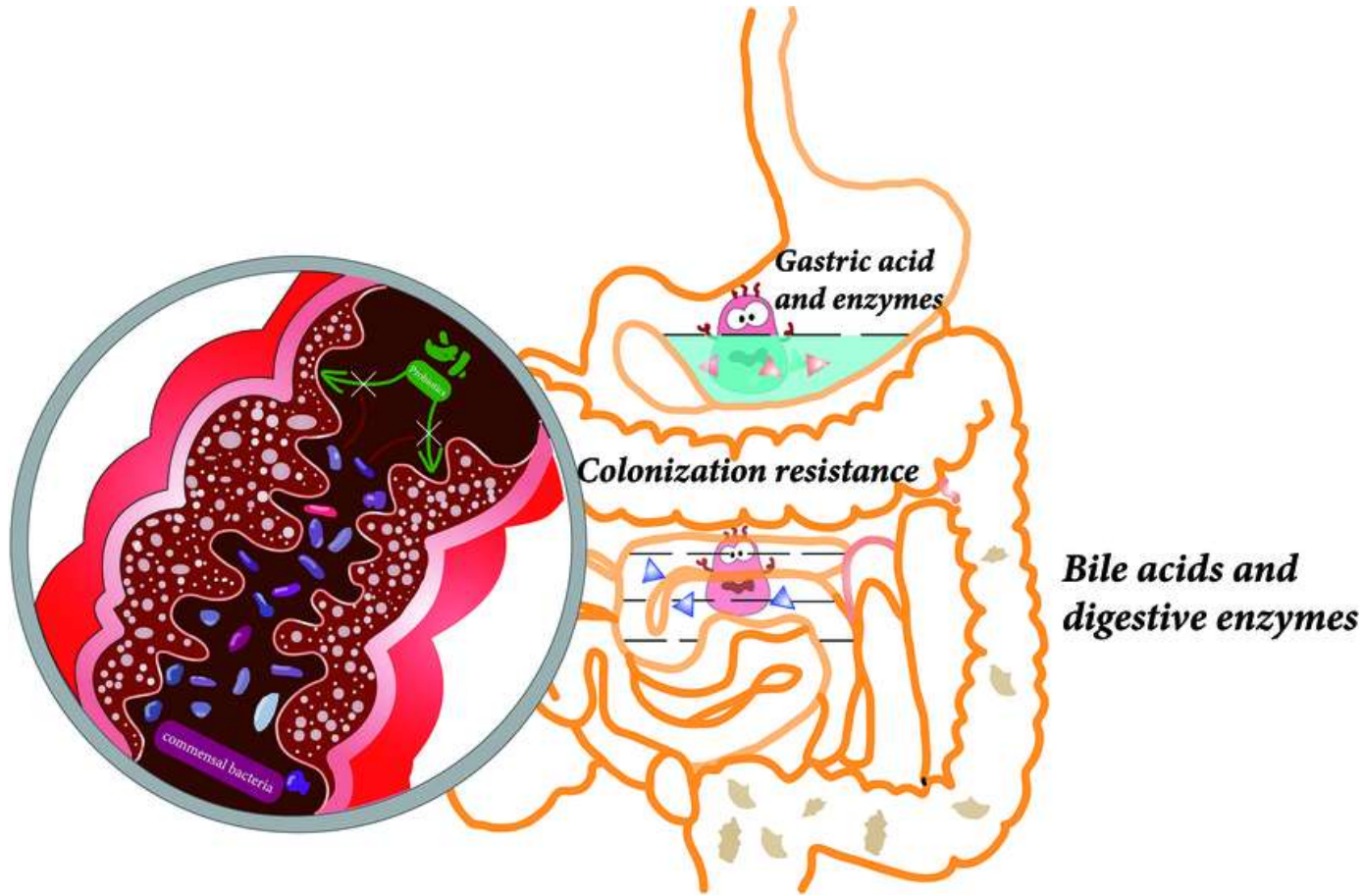

Total mentions
350
300
250
200
150
100
50
0
Postbiotics
Paraprobiotics
Non-viable probiotics
Heat-killed probiotics
Tyndallized probiotics

Antimicrobial substances

- Probiotics produce various antimicrobial acting substances
- Examples: lactic acid, hydrogen peroxide, microcines, deconjugated bile acids [Oelschlaeger, 2010], bacteriocins [Maqueda et al., 2008]
- Antibiotics also produced by probiotics → reuterin:
  - Broad-spectrum antibiotic
  - Active against yeast, gram-positive and gram-negative bacteria, fungi, viruses, protozoa
  - Produced by strain ATCC55730 from L. reuteri [Cleusix et al., 2007]

Species

- Lactobacilli:
  - Present in GIT, oral cavity and vagina of humans [Walter, 2008]
  - Widespread use in production and fermentation of foods → ability to convert hexose sugars to lactic acid → preservation [Fijan, 2014]
  - Excellent for use as probiotics: high tolerance to acid and bile, capability to adhere to intestinal surfaces [Tulumoglu et al., 2013]
- Bifidobacteria:
  - First colonizers of the human gut together with lactobacilli [Turroni et al., 2012]
  - Well known for resistance against bile salts [Fijan, 2014]


Gastric acid
and enzymes
Colonization resistance
Bile acids and
digestive enzymes
commensal bacteria

Species

- Bacillus species:
  - Either spore-forming aerobic or facultative aerobic, gram positive bacteria
  - B. subtilis, B. cereus, B. coagulans are members with probiotic characteristics [Fijan, 2014]
- Eschericha coli Nissle 1917:
  - Able to colonize the gut and compete with resident and pathogenic bacteria through multiple fitness factors [Behnsen et al., 2013]
  - Stimulation of epithelial defensin production → restoration of disturbed gut barrier
  - „Sealing effect“ on tight junctions of enterocytes [Sonnenborn and Schulze, 2009]

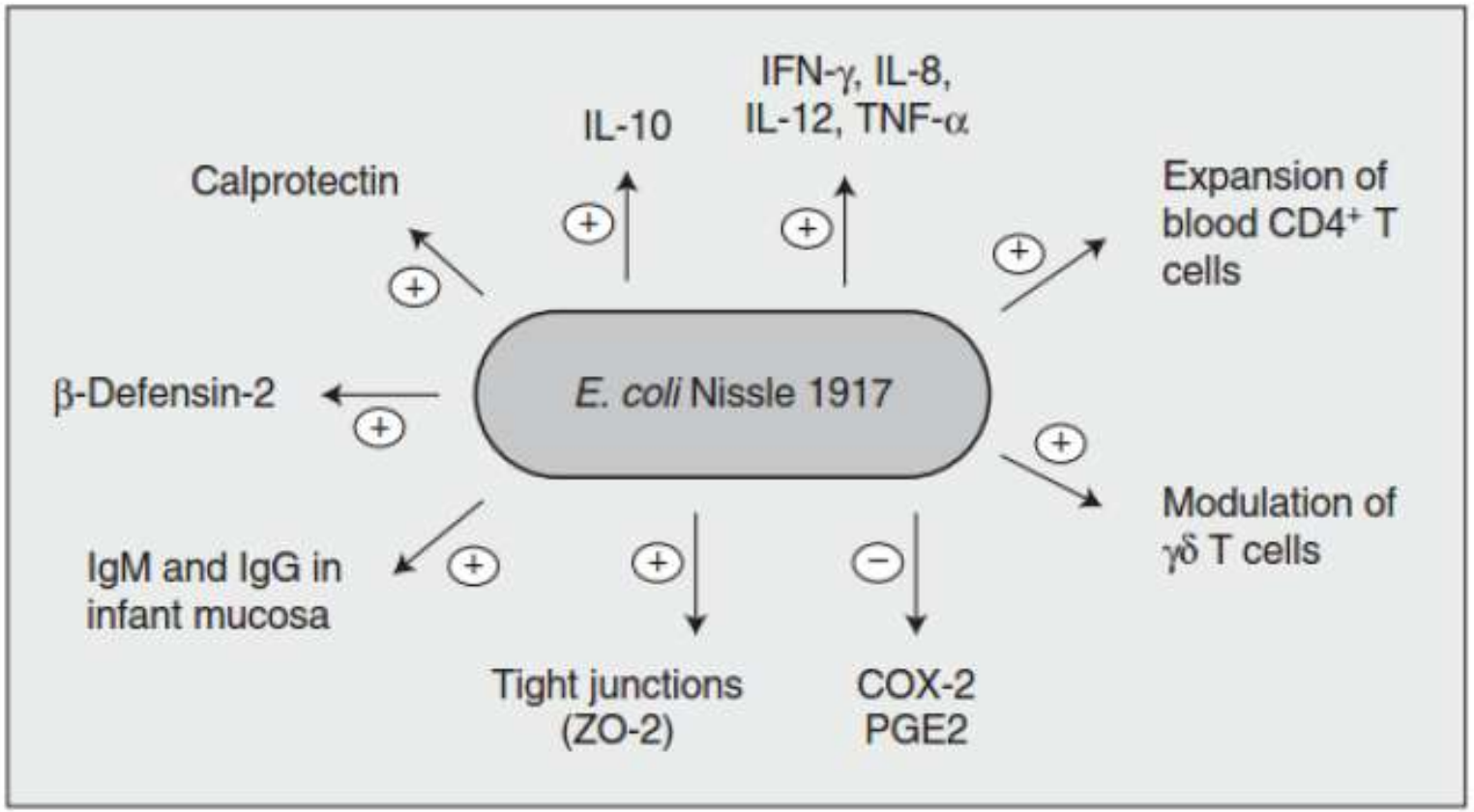


Figure 2. Various ways of immune modulation by E. coli Nissle 1917 (summary of data from in vitro and in vivo experiments) [Behnsen et al., 2013]

Table 2 Summary of recommendations for use of probiotics in diarrheal diseases

Condition	Proven efficacy	Probable efficacy
Acute infectious diarrhea		
Adults		
Treatment	*Lactobacillus rhamnosus* GG, *Saccharomyces boulardii* CNCM I-745	*Lactobacillus paracasei* B21060, *Lactobacillus reuteri* DSM17938
Children		
Treatment	*L. rhamnosus* GG, *S. boulardii* CNCM I-745	*Bacillus clausii*, *L. paracasei* B21060, *L. reuteri* DSM17938
Prevention		*L. rhamnosus* GG, *S. boulardii* CNCM I-745
Antibiotic-associated diarrhea		
Adults		
Treatment	*L. rhamnosus* GG, *S. boulardii* CNCM I-745	
Prevention	*Lactobacillus bulgaricus*, *Lactobacillus casei* DN-114001, *L. reuteri* ATCC 55730, *Streptococcus thermophilus*, and mixture of *Lactobacillus acidophilus* CL1285 + *L. casei* LBC80R + *L. rhamnosus* CLR2	
Children		
Treatment	*L. rhamnosus* GG, *S. boulardii* CNCM I-745	
Clostridium difficile-associated diarrhea		
Adults		
Prevention	Mixture of *L. acidophilus* CL1285 + *L. casei* LBC80R + *L. rhamnosus* CLR2, mixture of *Bifidobacterium bifidum* + *L. acidophilus*, *L. bulgaricus*, *L. casei* DN-114001, *L. casei* LBC80R, *S. thermophilus*	
Children		
Prevention		*S. boulardii* CNCM I-745
Traveler's diarrhea		
Adults		
Prevention	*S. boulardii* CNCM I-745	
Irritable bowel syndrome		
Adults		
Treatment	*Bifidobacterium infantis* 35 624, *Escherichia coli* DSM17252, *Lactobacillus plantarum* 299v, *S. boulardii* CNCM I-745	*B. bifidum* MIMBb75, VSL#3

Treatment of acute diarrhea with probiotics – meta-analyses

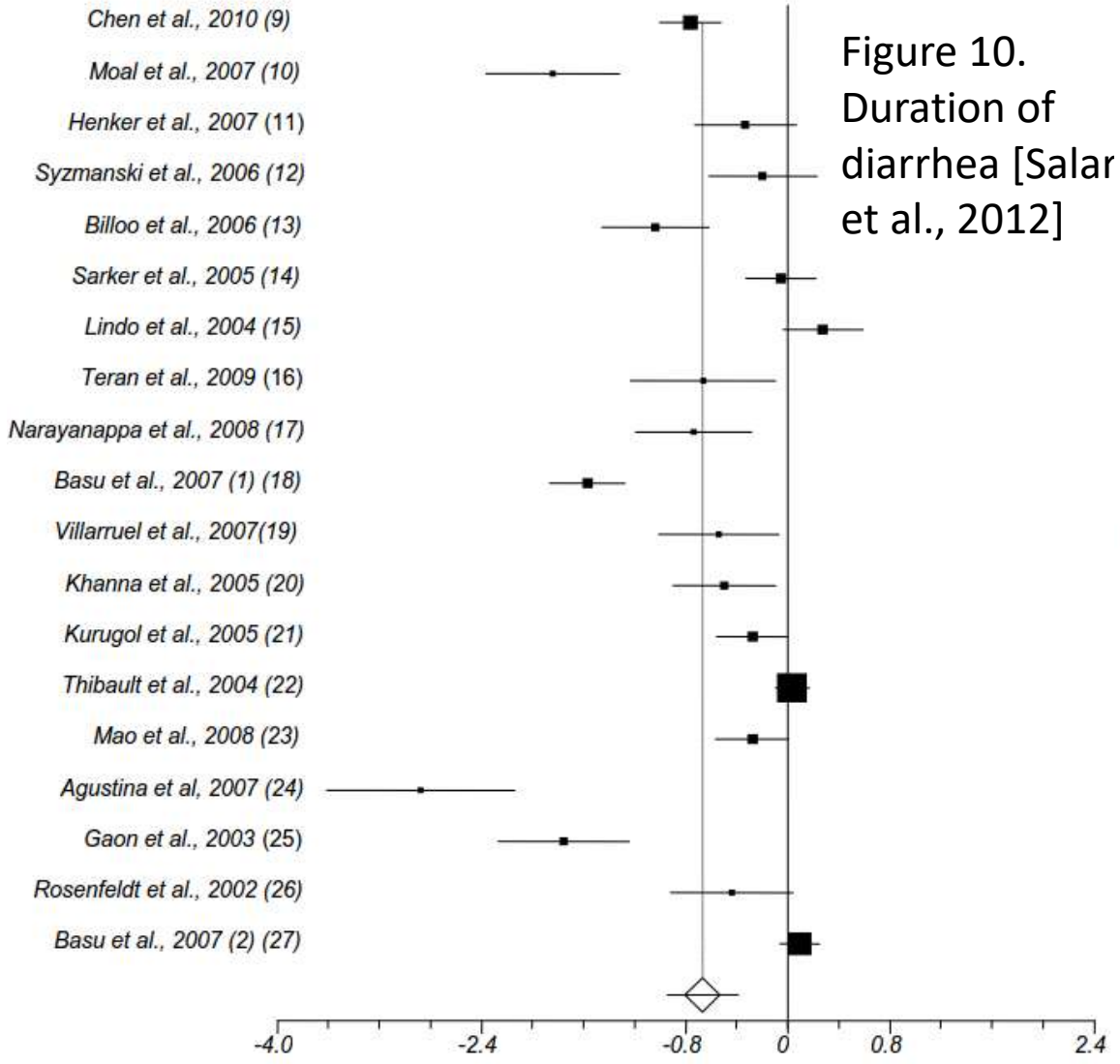


Figure 10. Duration of diarrhea [Salar et al., 2012]

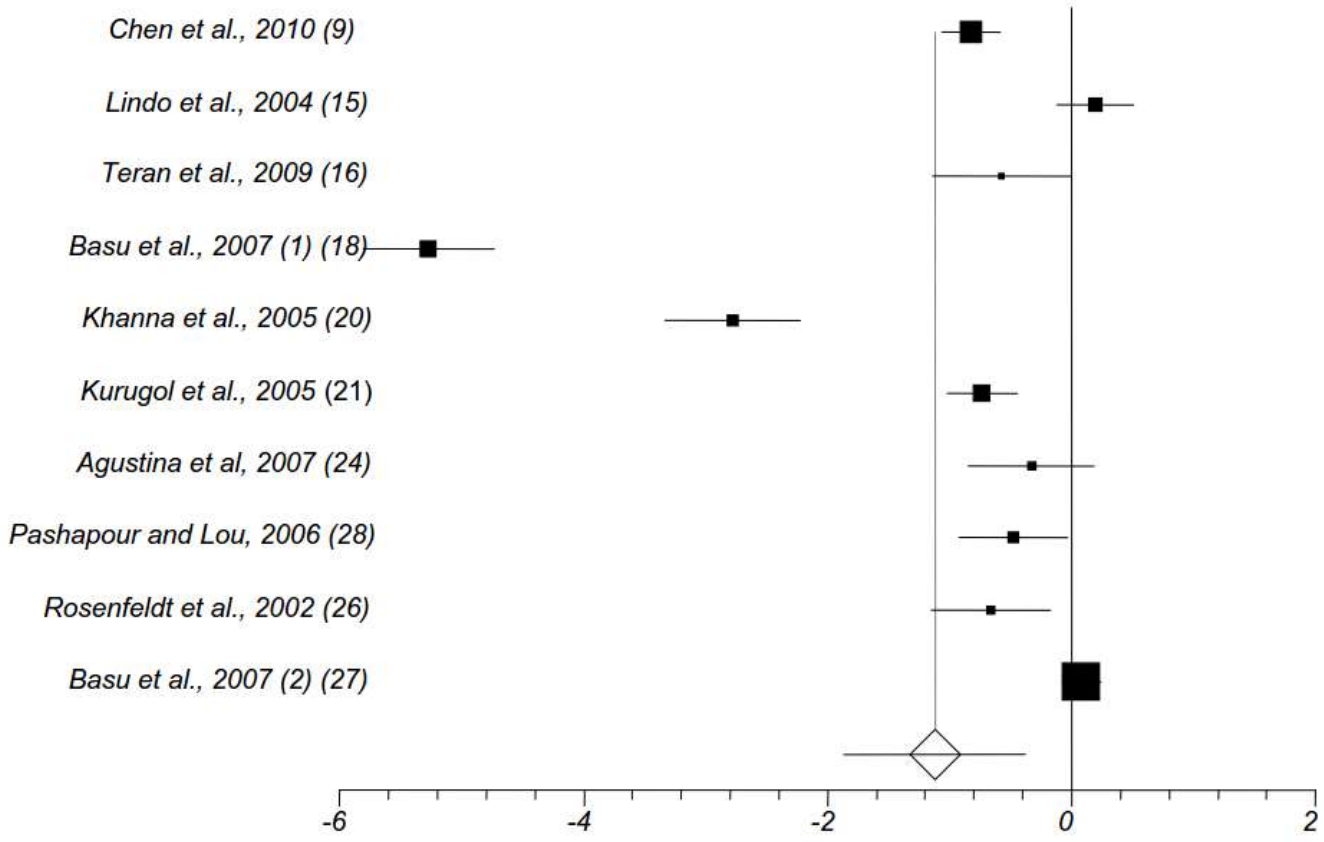
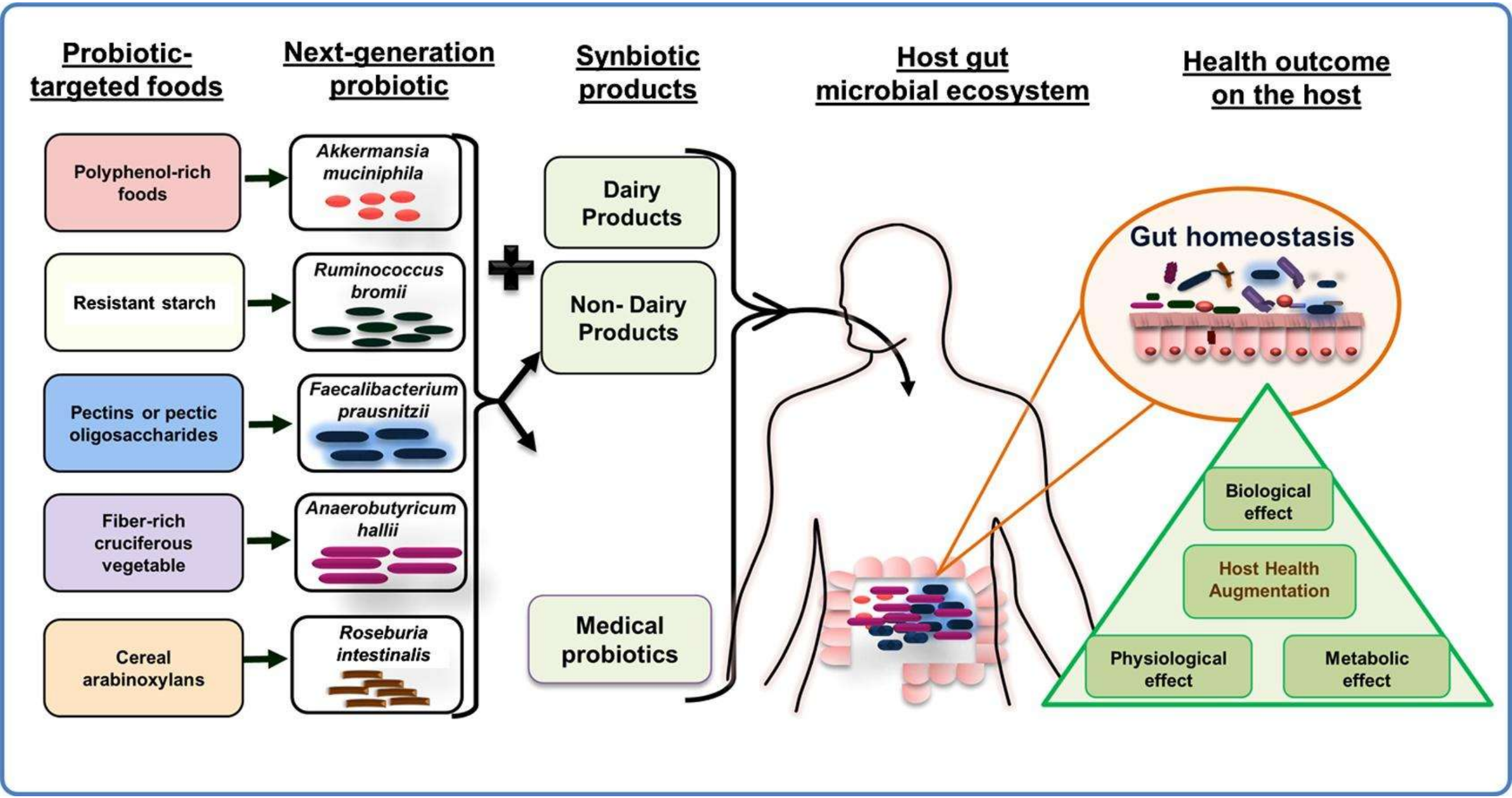


Figure 11. Duration of hospitalization [Salari et al., 2012]

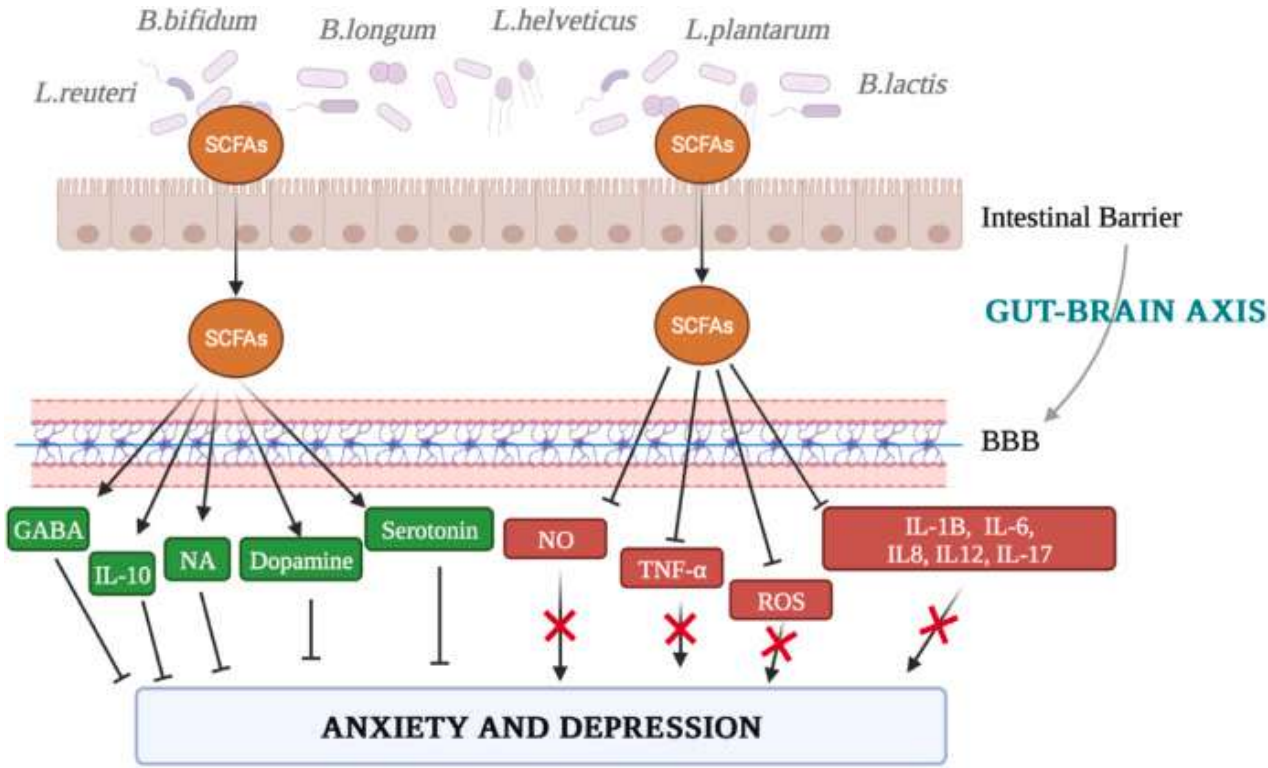
Methods: We conducted searches of MEDLINE, EMBASE, CENTRAL, PsycINFO, CINAHL, ProQuest, LILACS, and Web of Science up to February 2020 to identify randomized controlled trials (RCTs) investigating the efficacy of probiotics associated with or without pharmacological or psychological therapies for patient-important outcomes including relief of depressive, anxiety and stress symptoms, cognitive functions, adverse events and quality of life. We used the GRADE approach to rate the overall certainty of the evidence by outcome. The protocol of the systematic review was registered with PROPSERO and published under the number CRD4202016329.

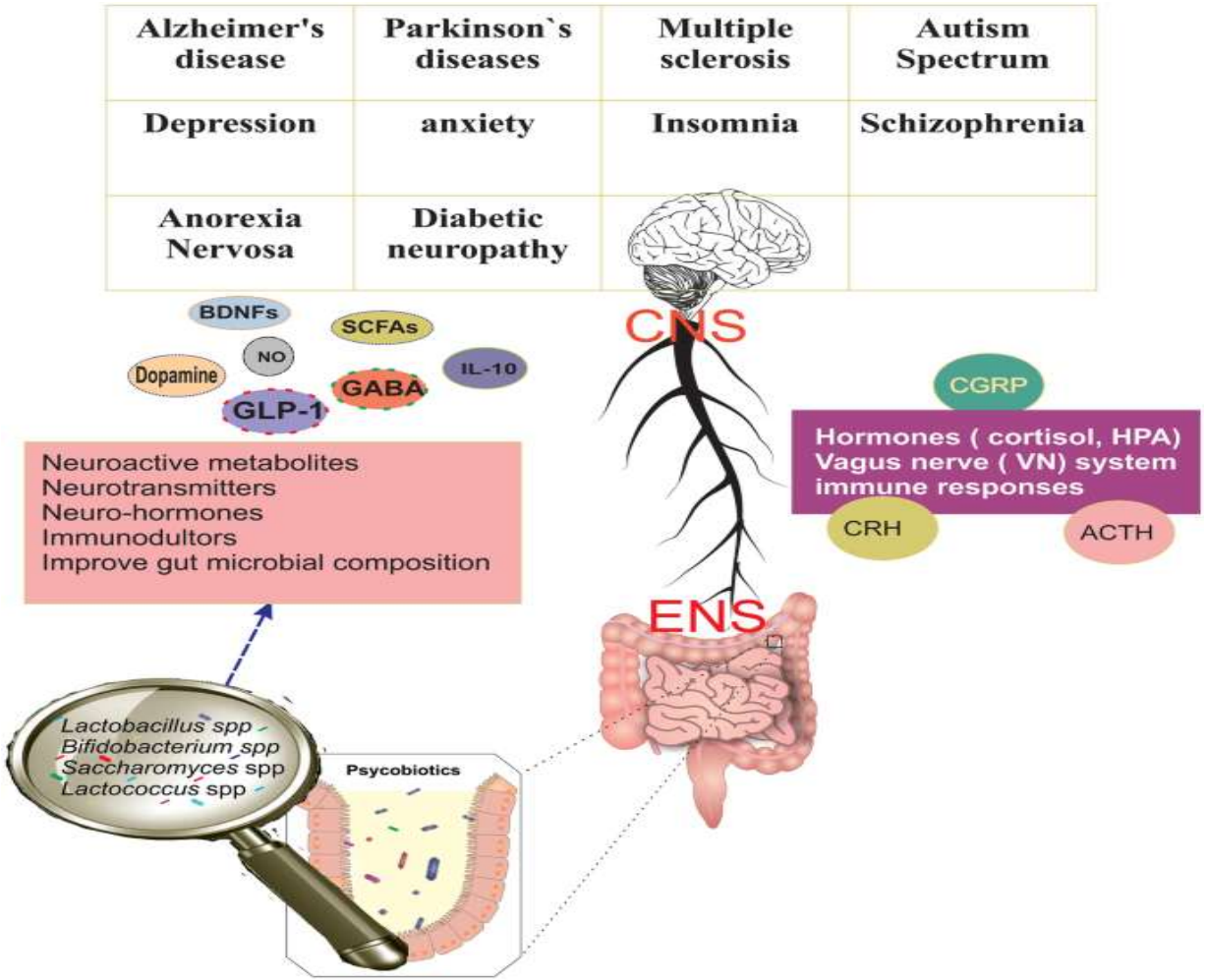
Results: 16 RCTs including 1,125 patients proved eligible. Results suggested a significant improvement in using Beck Depression Index (MD, -3.20 [95% CI, -5.91 to -0.49], p = 0.02; I2 = 21%, p = 0.28) for depression symptoms and State-Trait Anxiety Inventory (STAI) (MD, -6.88 [95% CI, -12.35 to -1.41], p = 0.01; I2 = 24%, p = 0.25) for anxiety with overall certainty in evidence rated as moderate and low, respectively. However, Depression Scale (DASS-Depression) (MD, 2.01 [95% CI, -0.80 to 4.82], p = 0.16; I2 = 0%, p = 0.62), Montgomery-Asberg Depression Rating Scale (MADRAS) (MD, -2,41 [95% CI, -10,55 to 5,72], p = 0,56; I2 = 87%, p = 0,006), Anxiety scale (DASS-Anxiety) (MD, 0.49 [95% CI, -4.05 to 5.02], p = 0.83; I2 = 74%, p = 0.05), and Stress Scale (DASS-Stress) (MD, 0.84 [95% CI, -2.64 to 4.33], p = 0.64; I2 = 34%, p = 0.22) showed no significant decrease in the relief of depression, anxiety and stress symptoms of probiotics compared to placebo with overall certainty in evidence rated as very low for all outcomes. We also found no differences in the Beck Anxiety Index (BAI) (MD, -3.21 [95% CI, -6.50 to 0.08], p = 0.06; I2 = 0%, p = 0.88) with overall certainty in evidence rated as low. Results suggested a non-statistically significantly effect of probiotics in the adverse events outcomes.

Conclusions: The current review suggests that probiotics may improve symptoms of depression and anxiety in clinical patients. However, given the limitations in the included studies, RCTs with long-term follow-up and large sample sizes are needed.

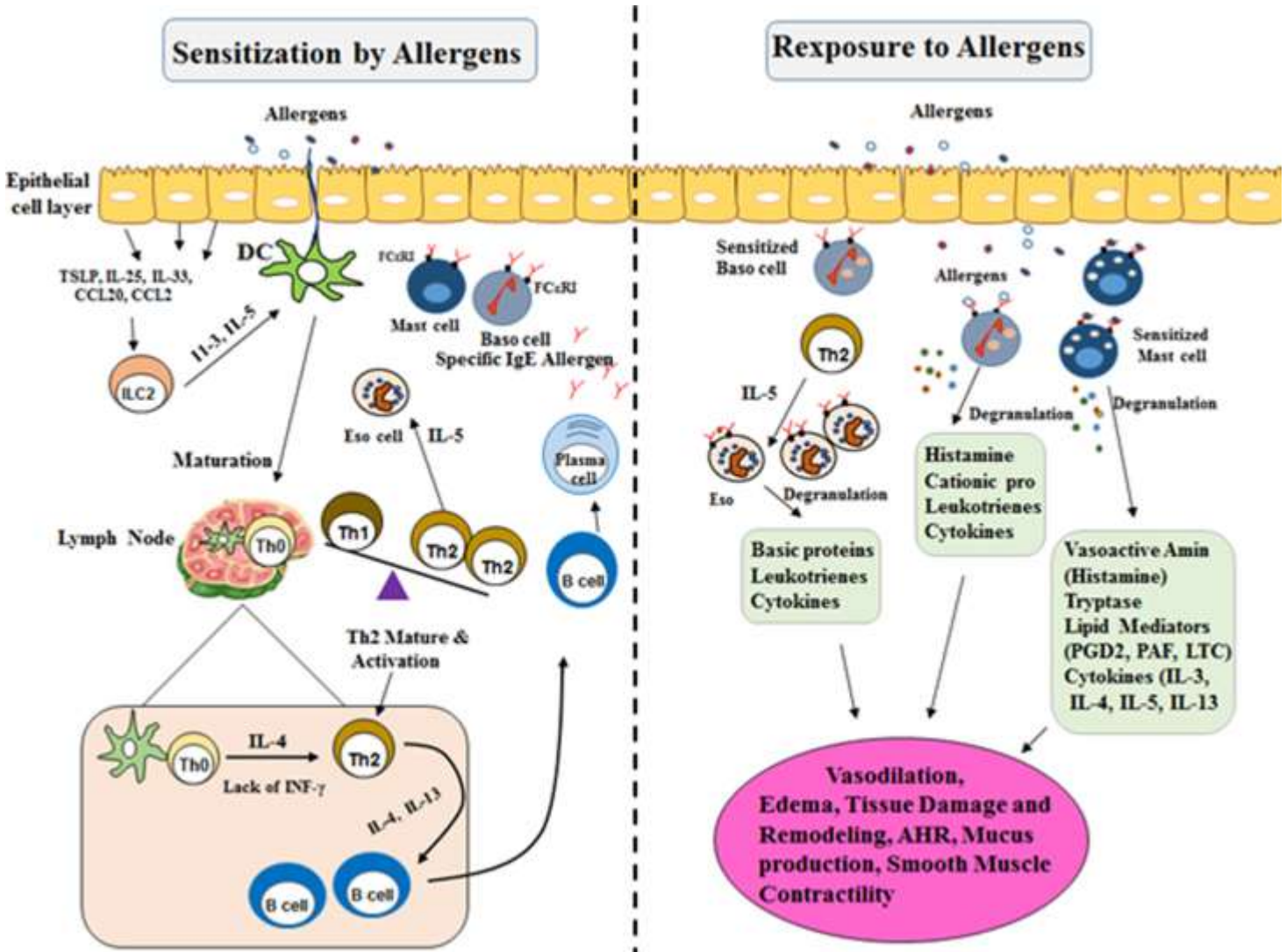

Probiotic-targeted foods
Next-generation probiotic
Synbiotic products
Host gut microbial ecosystem
Health outcome on the host
Polyphenol-rich foods
Resistant starch
Pectins or pectic oligosaccharides
Fiber-rich cruciferous vegetable
Cereal arabinoxylans
Akkermansia muciniphila
Ruminococcus bromii
Faecalibacterium prausnitzii
Anaerobutyricum hallii
Roseburia intestinalis
Dairy Products
Non- Dairy Products
Medical probiotics
Gut homeostasis
Biological effect
Host Health Augmentation
Physiological effect
Metabolic effect

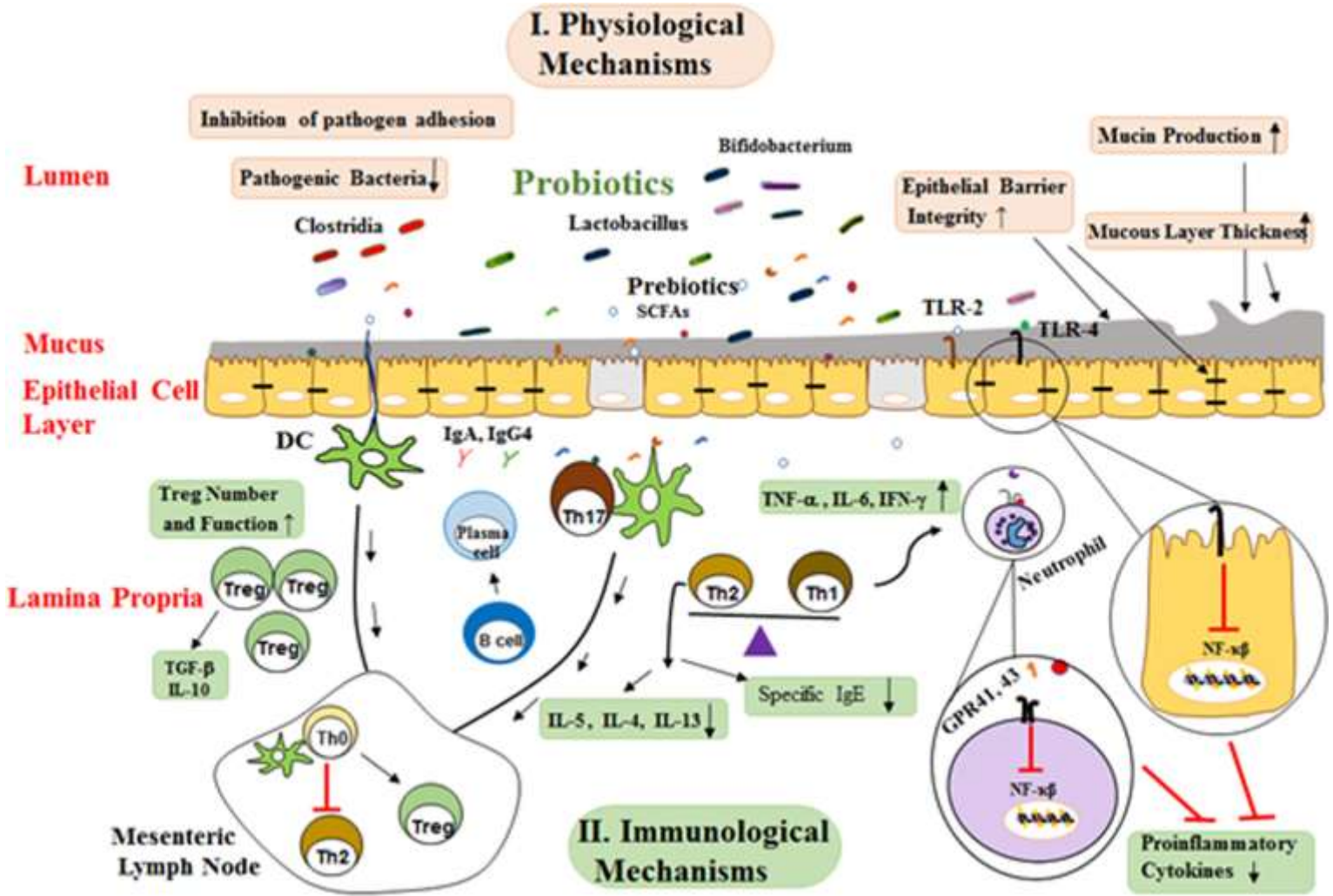
Probiotics and anxiety





a significant decrease in depressive symptoms favoring probiotics containing strains such as Lactobacillus acidophilus, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus salivarius, Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium breve, and Bifidobacterium longum (MD: -2.69, CI95%: -4.22/-1.16, p value: 0.00). Conversely, RCTs using HAMD showed a non-significant reduction in depressive symptoms (MD: -1.40, CI95%: -3.29/0.48, p value: 0.14). RCTs employing DASS and MADRS scales also showed no significant differences.


Sensitization by Allergens
Rexposure to Allergens
Allergens
Epithelial cell layer
DC
TSLP, IL-25, IL-33, CCL20, CCL2
ILC2
Il-3, IL-5
FCεRI
Mast cell
Baso cell
Specific IgE Allergen
Eso cell
IL-5
Maturation
Lymph Node
Th0
Th1
Th2
Th2
Plasma cell
B cell
Th2 Mature & Activation
IL-4
Lack of INF-γ
IL-4, IL-13
B cell
B cell
Sensitized Baso cell
Th2
IL-5
Eso
Degranulation
Basic proteins
Leukotrienes
Cytokines
Allergens
Degranulation
Histamine
Cationic pro
Leukotrienes
Cytokines
Sensitized Mast cell
Degranulation
Vasoactive Amin (Histamine)
Tryptase
Lipid Mediators (PGD2, PAF, LTC)
Cytokines (IL-3, IL-4, IL-5, IL-13
Vasodilation, Edema, Tissue Damage and Remodeling, AHR, Mucus production, Smooth Muscle Contractility


I. Physiological Mechanisms
Inhibition of pathogen adhesion
Lumen
Pathogenic Bacteria
Probiotics
Bifidobacterium
Clostridia
Lactobacillus
Prebiotics
SCFAs
Epithelial Barrier Integrity
Mucin Production
Mucous Layer Thickness
TLR-2
TLR-4
Mucus
Epithelial Cell Layer
DC
IgA, IgG4
Treg Number and Function
Plasma cell
Th17
TNF-α, IL-6, IFN-γ
Lamina Propria
Treg
Treg
Treg
B cell
Th2
Th1
Neutrophil
TGF-β
IL-10
Specific IgE
IL-5, IL-4, IL-13
Th0
Th2
Treg
Mesenteric Lymph Node
II. Immunological Mechanisms
GPR41, 43
NF-κβ
NF-κβ
Proinflammatory Cytokines

Beneficial Microbes, 2017; 8(2): 153-162

Wageningen Academic Publishers

Beneficial effects of *Lactobacillus casei* strain Shirota on academic stress-induced sleep disturbance in healthy adults: a double-blind, randomised, placebo-controlled trial

M. Takada[1#*], K. Nishida[2#], Y. Gondo[1], H. Kikuchi-Hayakawa[1], H. Ishikawa[1], K. Suda[1], M. Kawai[1], R. Hoshi[3], Y. Kuwano[2], K. Miyazaki[1] and K. Rokutan[2]

[1]Yakult Central Institute, 5-11 Izumi, Kunitachi, Tokyo 186-8650, Japan; [2]Department of Pathophysiology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto, Tokushima, Tokushima 770-8503, Japan; [3]Faculty of Research and Development, Yakult Honsha Co., Ltd., 1-1-19 Higashi-Shimbashi, Minato, Tokyo 105-8660, Japan; mai-takada@yakult.co.jp; [#]These authors contributed equally to this work

Received: 21 August 2016 / Accepted: 16 December 2016

RESEARCH ARTICLE

Abstract

The present study examined whether *Lactobacillus casei* strain Shirota (LcS) improves sleep quality under psychological stress. A double-blind, placebo-controlled trial was conducted in healthy 4th year medical students exposed to academic examination stress. The trial was repeated over two consecutive years in different groups of students, and the data were pooled. For 8 weeks prior to and 3 weeks after a national standardised examination, a total of 48 and 46 subjects received a daily dose of 100 ml of LcS-fermented milk or non-fermented placebo milk, respectively. Study measures included subjective anxiety, overnight single-channel electroencephalography (EEG) recordings, and the Oguri-Shirakawa-Azumi (OSA) sleep inventory scores of subjective sleep quality. Total OSA scores were significantly lower than baseline on the day before the exam and recovered after the exam, indicating a stress-induced decline in sleep quality. There was a significant positive effect of LcS treatment on OSA factors for sleepiness on

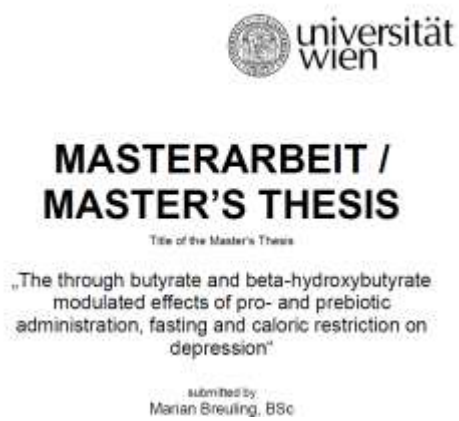
Meta-analysis probiotic allergy

Methods
We performed a comprehensive search on PubMed, Cochrane Library, EMBASE for relevant publications from 1 Jan 2000 to 1 July 2021. Physical examinations, Pediatric Rhinoconjunctivitis Quality of Life Questionnaires (PRQLQs), Total Nasal Symptom Score (TNSS), Nasal or Eye Symptom Score (NSS or ESS), serum allergen-specific IgE, and eosinophil were used as evaluating indicators for AR and allergic asthma in children and adolescents. The meta-analysis was performed using Review Manager (RevMan, Version 5.3).
Results
15 randomized controlled trials (RCTs) with a total of 1388 participants were included for the meta-analysis. Among them, 729 patients treated with probiotics served as the probiotics group, and 659 patients with placebo as control group. Significantly greater reduction in PRQLQs from baseline to endpoint (SMD = −2.57, 95% CI [− 4.66, −0.48] $P < 0.01$), NSS (SMD = −1.43, 95% CI [− 1.63, − 1.23], $P < 0.01$) and ESS (total MD = −1.67, 95% CI [− 1.79, − 1.55], $P < 0.01$) were observed in probiotics group compared to control group. Probiotics have no significant effect to serum IgE and eosinophils ($P > 0.01$).
Conclusion
The results of this meta-analysis indicated that probiotics treatment may reduce PRQLQs, NSS, ESS in patients with allergic airway disease. More research involving the mechanism of probiotics are needed to clarify the role of probiotics in AR and allergic asthma in children and adolescents.

Probiotics effect the Epigenetic regulation

The novel probiotic approach consisting of Lactobacillus plantarum, Saccharomyces cerevisiae var. boulardii and oc-tacosanol)had a positive effect on regulating the expression of certain miRNAs and mRNAs important for regulating inflammation and adipogenesis, which are essential for obesity onset and control. , in print

Pro-, prebiotika und SCFAS


universität wien

MASTERARBEIT / MASTER'S THESIS

Title of the Master's Thesis

„The through butyrate and beta-hydroxybutyrate modulated effects of pro- and prebiotic administration, fasting and caloric restriction on depression"

submitted by
Marian Breuling, BSc

Butyrate and beta-hydroxybutyrate are similar due to their structure and additionally seem to have similar physiological influencing properties. That's why literature was obtained examining their effects on depression through fasting, caloric restriction and pre- and probiotic administration. A meta-analysis was conducted with the three included pre-and probiotic intervention trails and is able to show a significant increase of butyrate (SMD 0,34; [0,02 – 0,67]) and an improvement of depression scores (SMD 0,15, [-0,35 - 0,70]) through the pre-and probiotic interventions. Furthermore, a correlation between butyrate and depression scores (b1 = 1,57; p = 0,17) was calculated, which suggests a connection between butyrate and depression, as well as pre- and probiotic administration as possible depression ameliorating intervention. Additionally, three studies were qualitatively analyzed examining fasting as intervention. A possible connection between fasting, betahydroxybutyrate and depression was found. Caloric restriction as potential long-term intervention was mentioned as alternative as well as further needed studies stated.

Prok

ILSI EUROPE

ILSI Entities | English

About us | Community | Activities | Events | Publications | Contact

Prediction of individual responses to prebiotics and probiotics intervention

A Prebiotics and Probiotics Task Forces' collaboration

Background and Objectives

Individuals show a broad range of responses to dietary interventions and vary widely in their susceptibility to nutritional challenges or stressors. Consequently, anticipating individual-specific responses to a given pre- or probiotic intervention and selection of the most appropriate target population for demonstrating the benefits of such an intervention is challenging. This activity will review state-of-the-art in silico, in vitro, and in vivo approaches for the rational design and testing of personalised interventions. The main objective is to provide a path forward, highlighting tools and approaches that enable personalised pre/probiotic interventions that improve human health and well-being.

Probiotics, new ways

Letter | Published: 01 July 2019

Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study

Clara Depommier, Amandine Everard, Céline Druart, Hubert Plovier, Matthias Van Hul, Sara Vieira-Silva, Gwen Falony, Jeroen Raes, Dominique Maiter, Nathalie M. Delzenne, Marie de Barsy, Audrey Loumaye, Michel P. Hermans, Jean-Paul Thissen, Willem M. de Vos & Patrice D. Cani

Nature Medicine **25**, 1096–1103 (2019) | Cite this article

Probiotika: Sind tote Bakterien wirksamer als lebende?

Das Prinzip von Probiotika kennt jeder – egal ob als Joghurt oder Supplement: Dem Körper werden mit der Nahrung Bakterien zugeführt, die sich im Darm vermehren und gesundheitsförderlich sein sollen. Soweit die Theorie. Doch eine aktuelle Studie wirft Fragen auf.

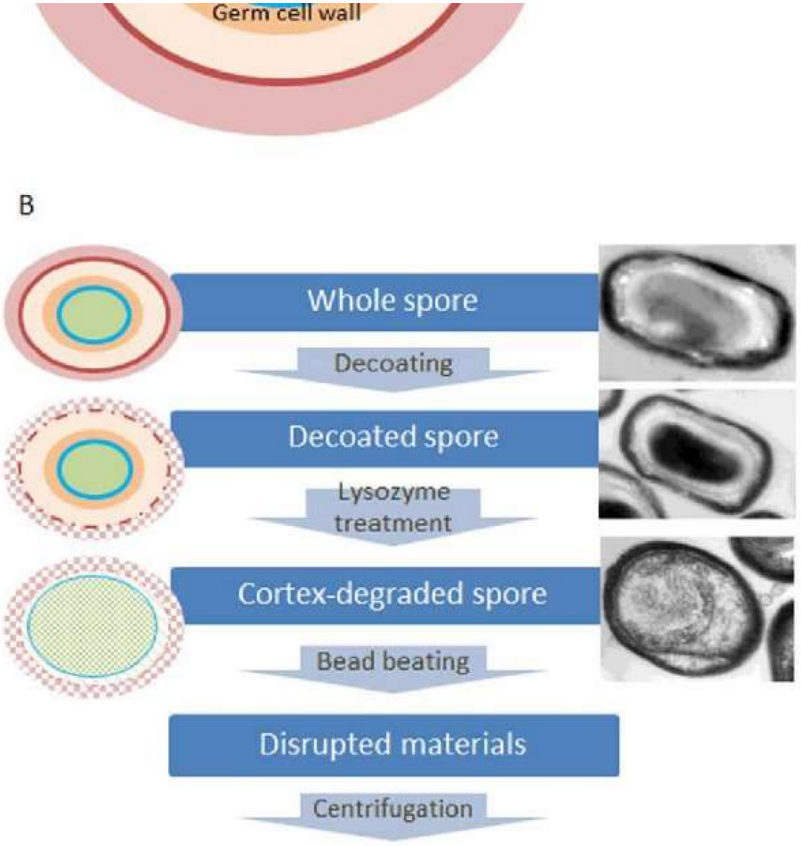
Commensal Obligate Anaerobic Bacteria and Health: Production, Storage, and Delivery Strategies

José Carlos Andrade[1†], Diana Almeida[2†], Melany Domingos[1], Catarina Leal Seabra[2†], Daniela Machado[1], Ana Cristina Freitas[2*] and Ana Maria Gomes[2]

[1]CESPU, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, Gandra, Portugal
[2]CBQF - Centro de Biotecnologia e Química Fina - Laboratório Associado, Escola Superior de Biotecnologia, Universidade Católica Portuguesa, Porto, Portugal

In the last years several human commensals have emerged from the gut microbiota studies as potential probiotics or therapeutic agents. Strains of human gut inhabitants such as *Akkermansia*, *Bacteroides*, or *Faecalibacterium* have shown several interesting bioactivities and are thus currently being considered as food supplements or as live biotherapeutics, as is already the case with other human commensals such as bifidobacteria. The large-scale use of

Spores



The ingredient

According to Deerland, DE111 is a genome sequenced strain of *Bacillus subtilis*. The genome sequencing confirmed the strain contained no plasmids, antibiotic resistant or deleterious genes; the human clinical studies showed the strain's ability to control microbial populations, aid in digestion and maintain general health. Because the strain is a spore former it remains viable under a wide temperature and pH range, making it ideal for use in supplements as well as food and beverages.

Source: *Journal of Probiotics & Health*
2017, 5:4, doi: 10.4172/2329-8901.1000189
"The Effect of Bacillus subtilis *DE111 on the Daily Bowel Movement Profile for People with Occasional Gastrointestinal Irregularity"*
Authors: A.M. Cuentas et al.

Butyrate production or cross feeding ?

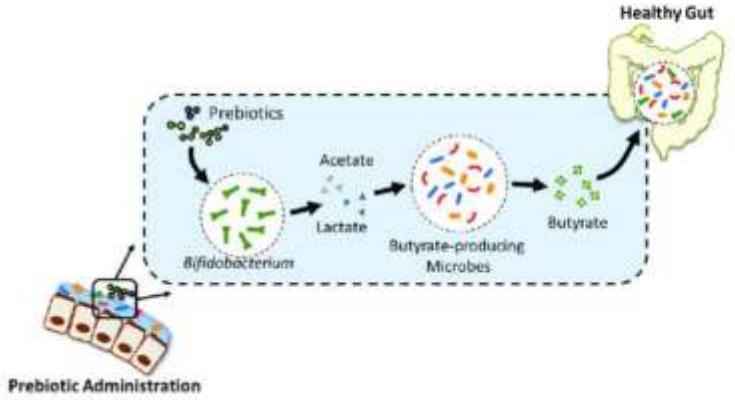
OPEN ACCESS Freely available online

PLOS ONE

Butyrate-Producing Probiotics Reduce Nonalcoholic Fatty Liver Disease Progression in Rats: New Insight into the Probiotics for the Gut-Liver Axis

Hitoshi Endo[1*], Maki Niioka[2], Noriko Kobayashi[3], Mamoru Tanaka[3], Tetsu Watanabe[1*]

1 Center for Molecular Prevention and Environmental Medicine, Department of Community Health, Tokyo University School of Medicine, Isehara, Japan, 2 Healthcare and

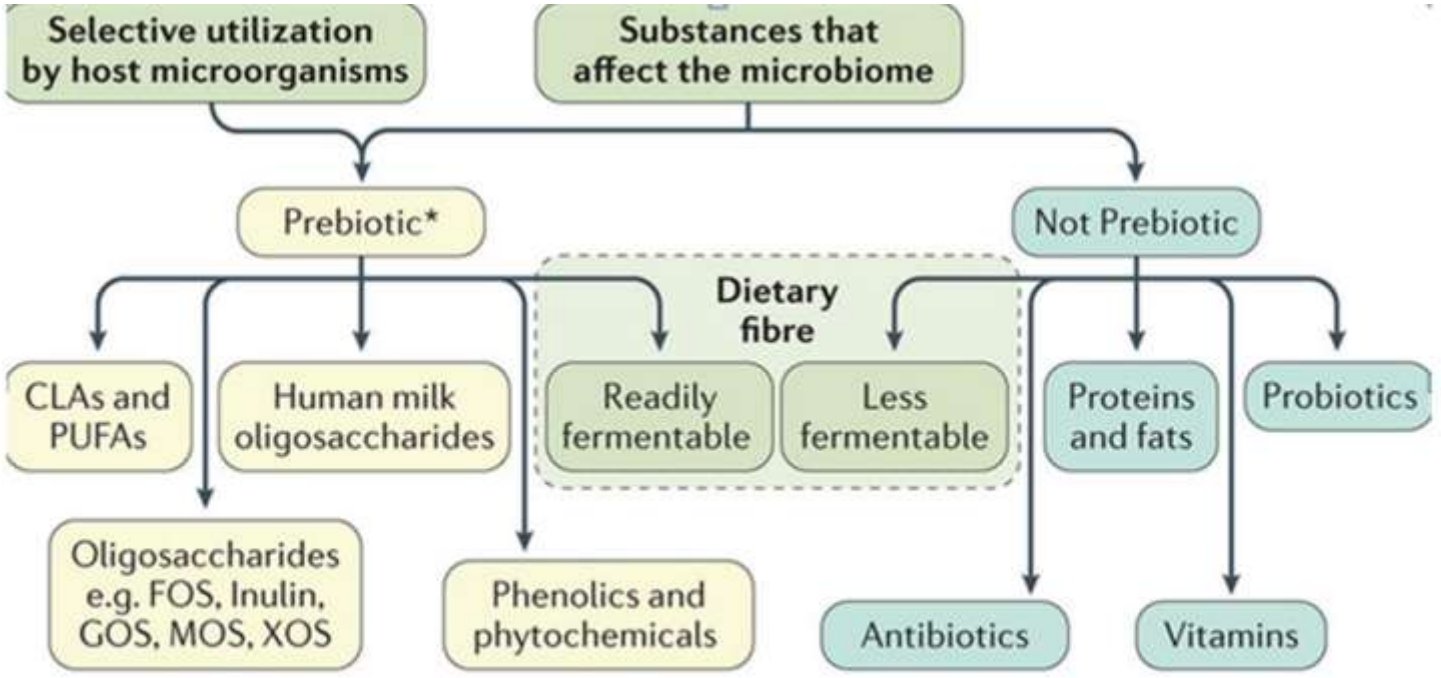


Figure

Caption

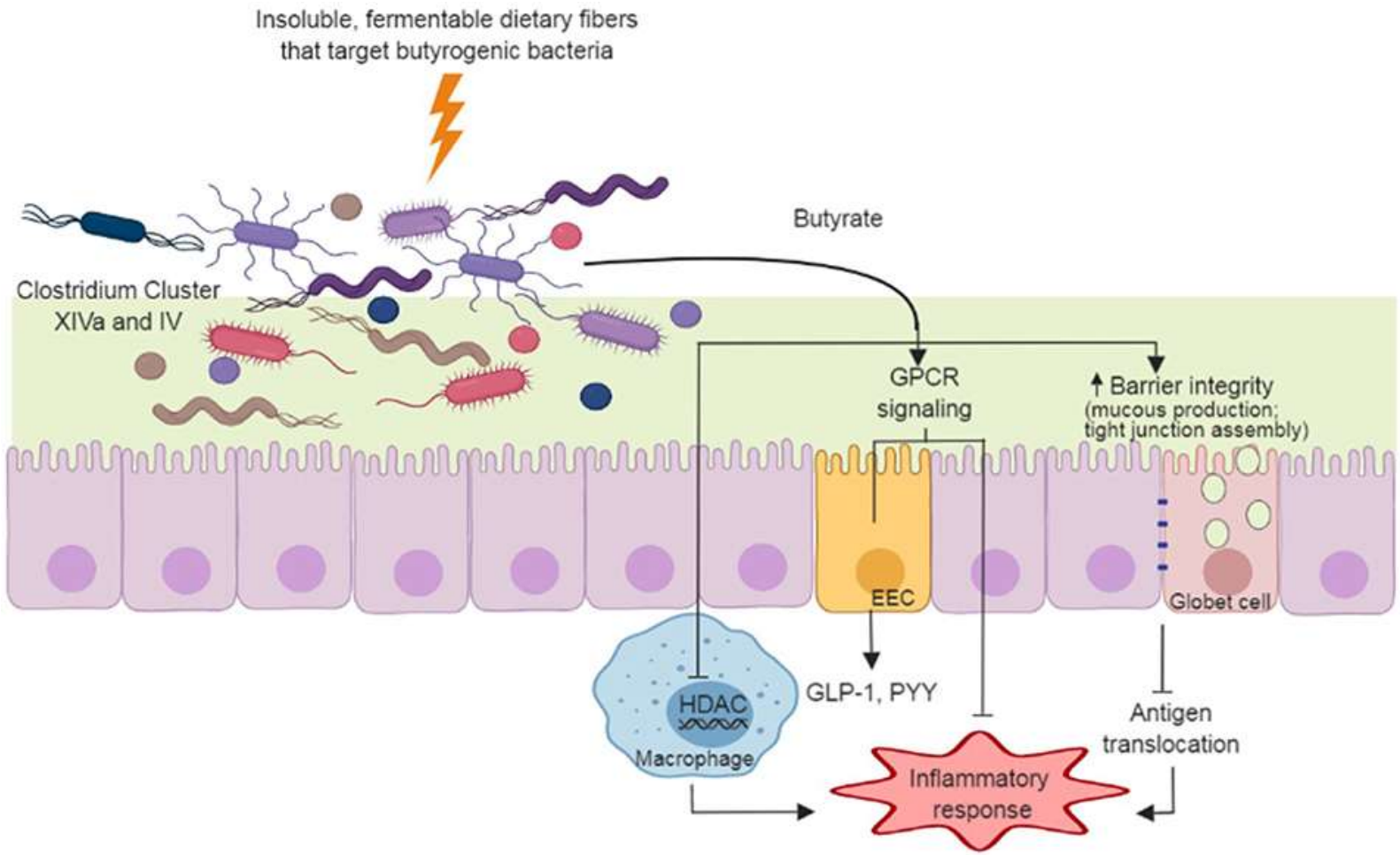
Figure 2. Cross-feeding effect between Bifidobacterium and butyrate-producing bacteria. Bifidobacterium utilises supplemented prebiotics, which stimulates their growth. Acetate produced by Bifidobacterium becomes a carbon source for butyrate-producing microbes, stimulating their growth and butyrate-producing activities and, in turn, modulating the ... Read more

Prebiotics what is it?

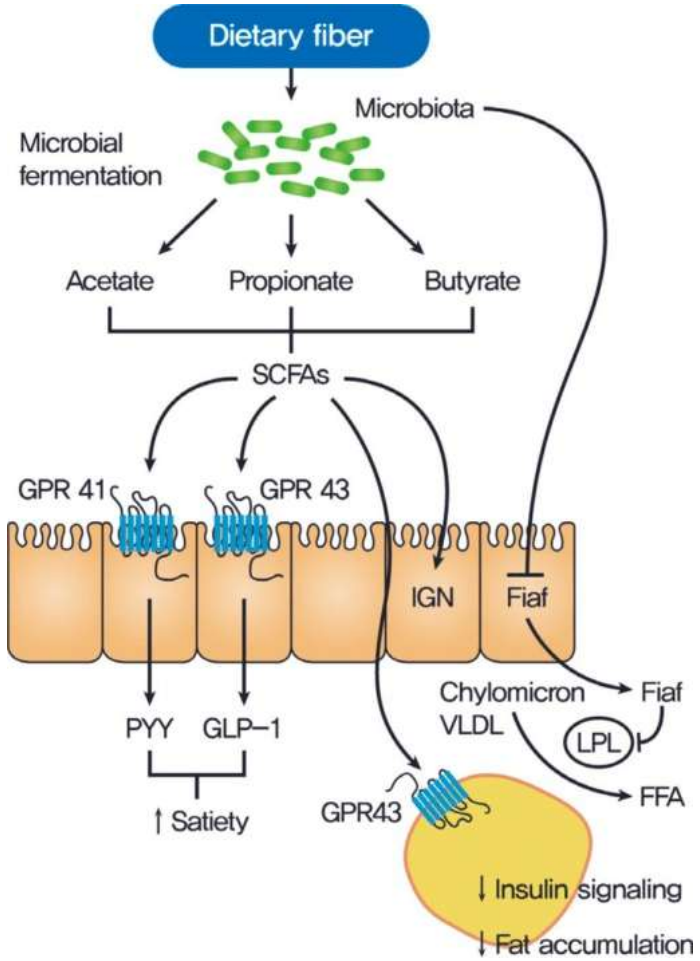


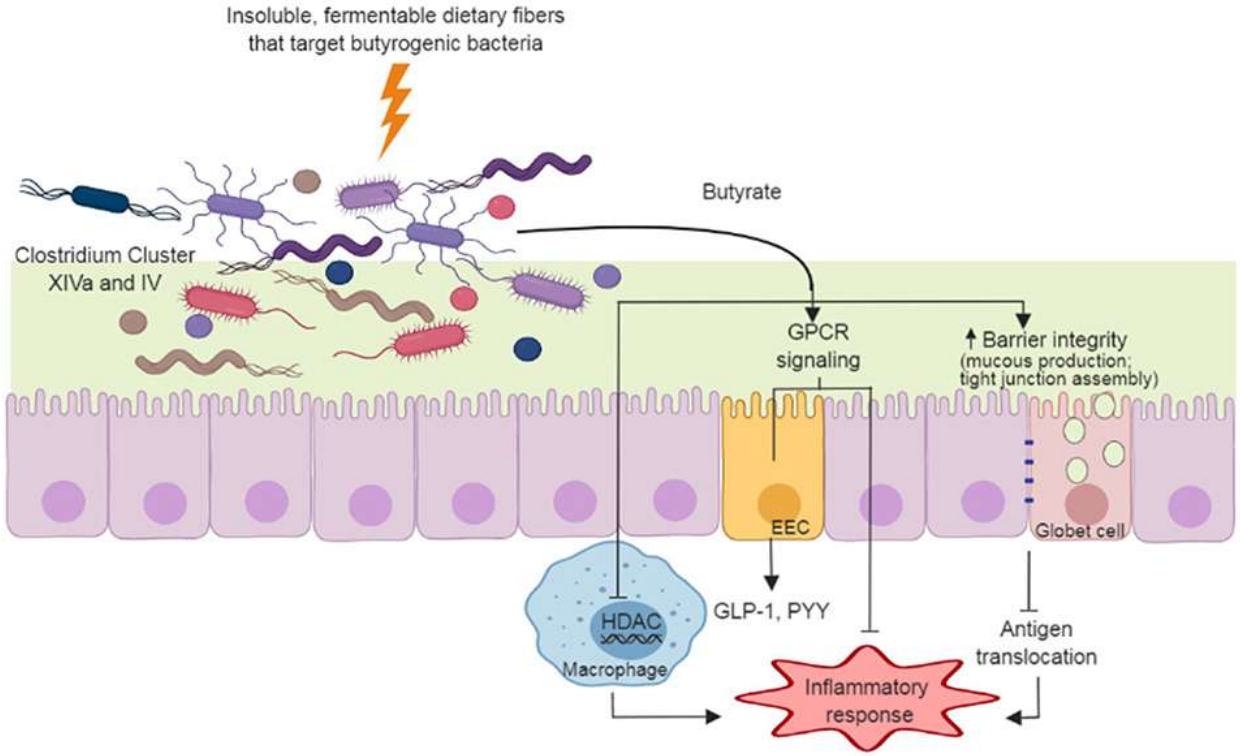
Credit: Gibson GR, et al. Nature Reviews Gastroenterology & Hepatology. 2017; 14: 491–502. (CC-BY)

Fibers and SCFA



Fibers and obesity, butyrogenic





Receptors of SCFAs

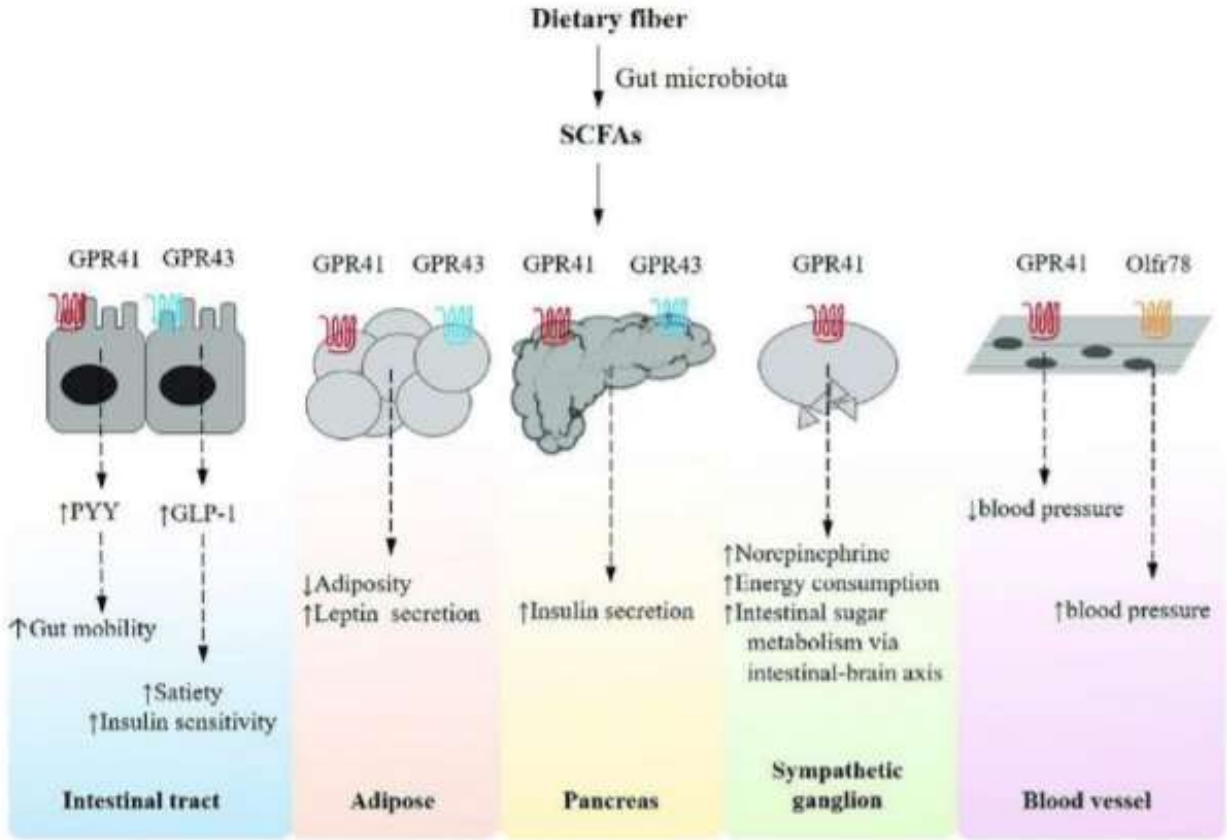
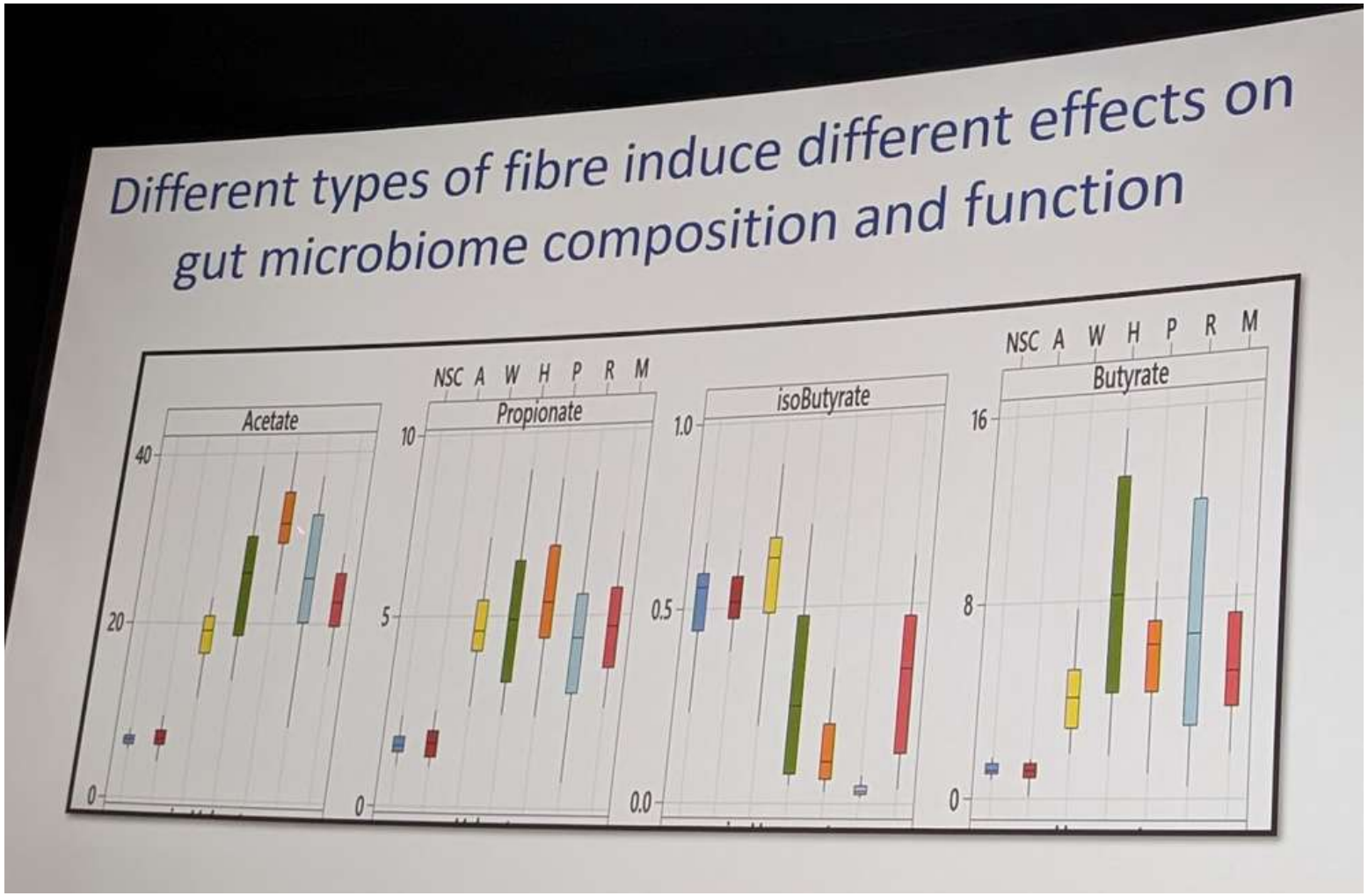
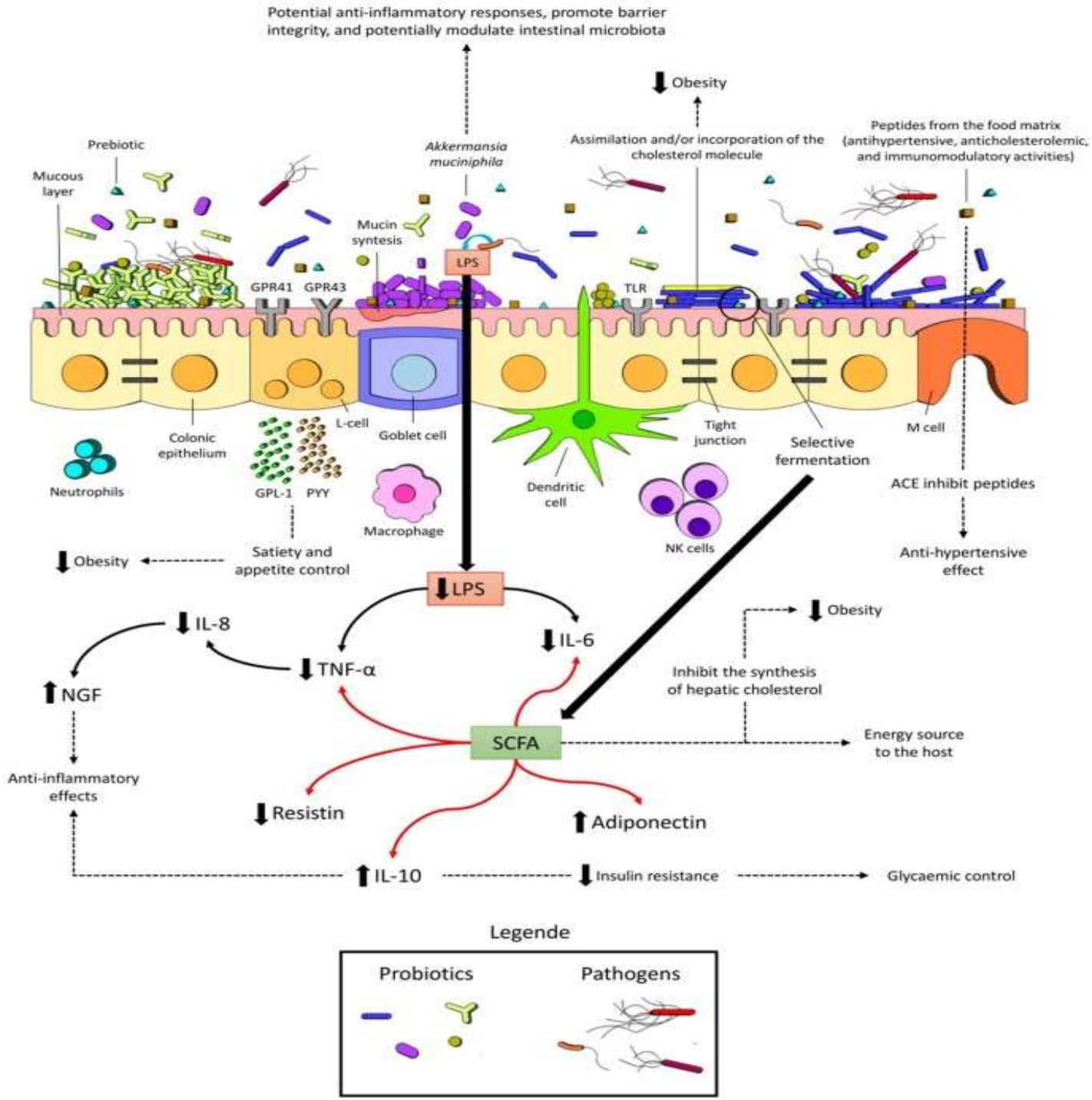
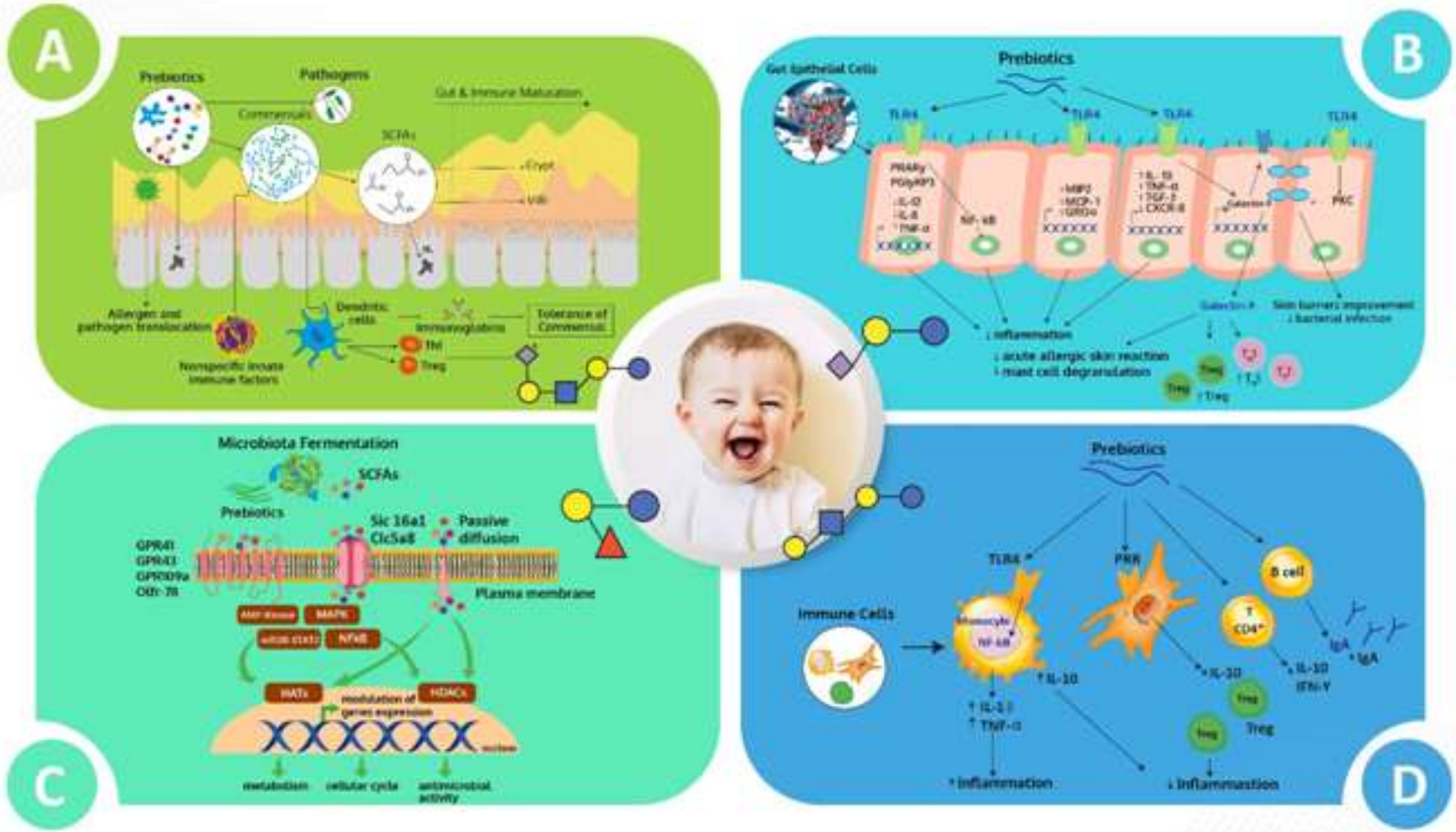
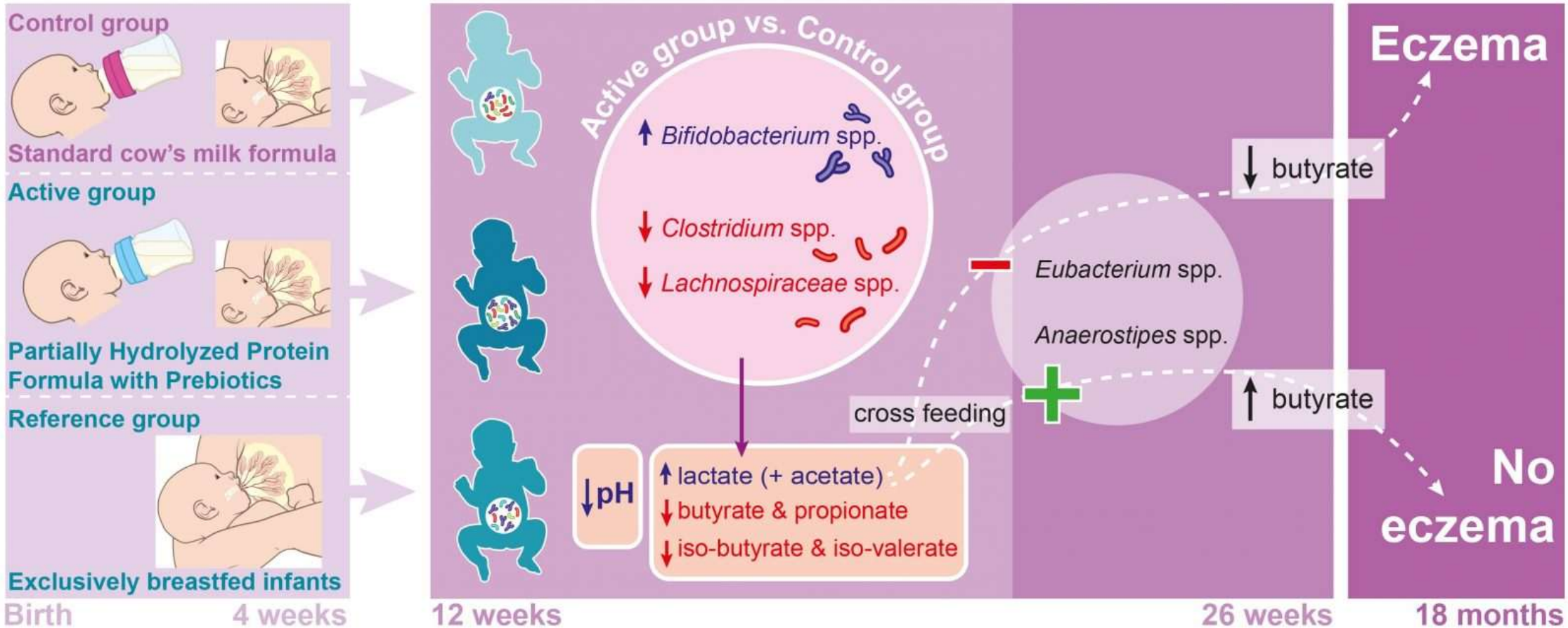


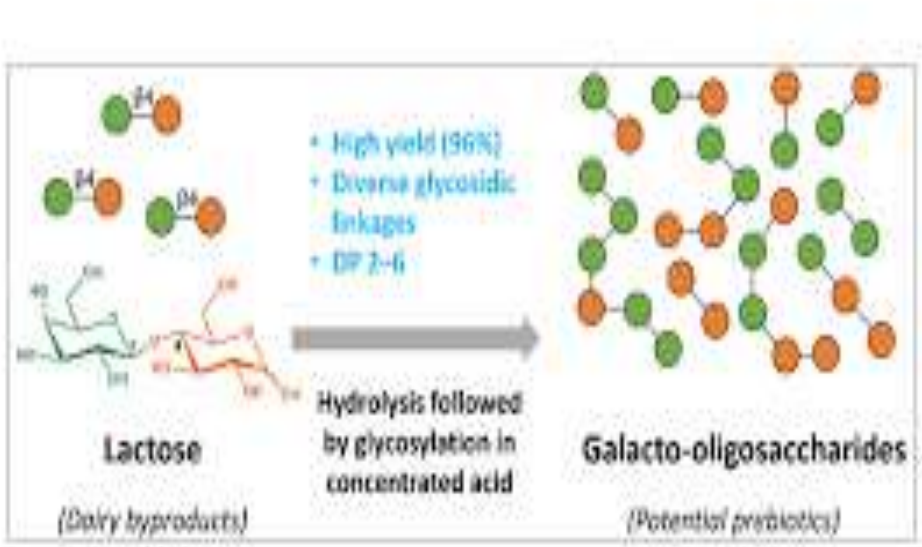
Figure 17. Short-chain fatty acid (SCFA)-receptor-mediated pathways and their effects on host energy metabolism in peripheral tissues. Gut microbes can ferment dietary fiber into SCFAs, which induce an array of G-protein coupled receptor-mediated signaling pathways that are essentially implicated in host energy homeostasis in multiple tissues [158].


Different types of fibre induce different effects on gut microbiome composition and function
NSC A W H P R M
Acetate
40
20
0
Propionate
10
5
0
isoButyrate
1.0
0.5
0.0
Butyrate
16
8
0

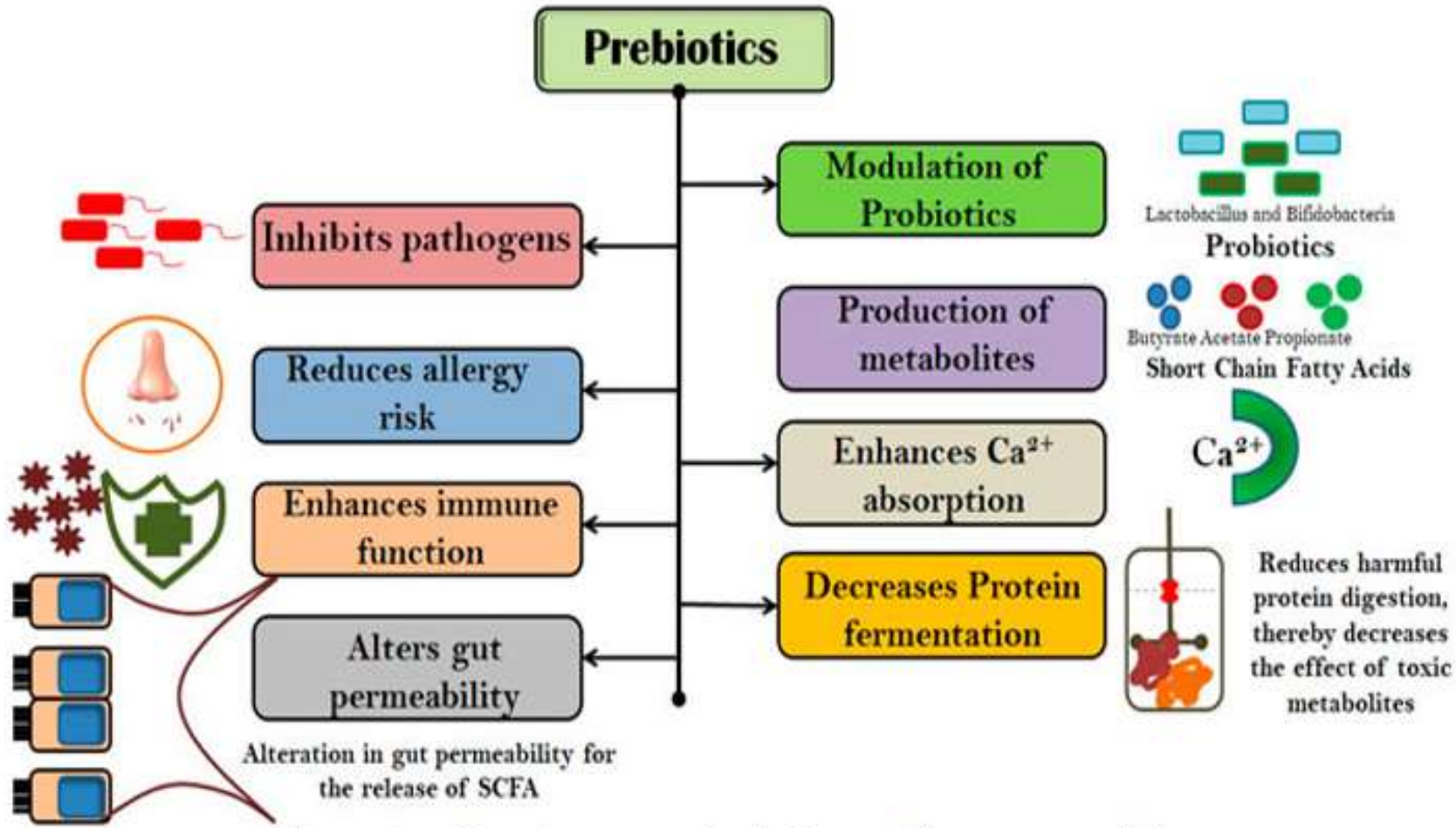

Potential anti-inflammatory responses, promote barrier integrity, and potentially modulate intestinal microbiota
Obesity
Prebiotic
Mucous layer
Akkermansia muciniphila
Assimilation and/or incorporation of the cholesterol molecule
Peptides from the food matrix (antihypertensive, anticholesterolemic, and immunomodulatory activities)
Mucin syntesis
LPS
GPR41
GPR43
TLR
Colonic epithelium
L-cell
Goblet cell
Tight junction
Selective fermentation
M cell
Neutrophils
GPL-1
PYY
Macrophage
Dendritic cell
NK cells
ACE inhibit peptides
Obesity
Satiety and appetite control
Anti-hypertensive effect
LPS
IL-8
IL-6
TNF-α
Obesity
NGF
Inhibit the synthesis of hepatic cholesterol
SCFA
Energy source to the host
Anti-inflammatory effects
Resistin
Adiponectin
IL-10
Insulin resistance
Glycaemic control
Legende
Probiotics
Pathogens


A
Prebiotics
Pathogens
Gut & Immune Maturation
Commensals
SCFAs
Crypt
Villi
Allergen and pathogen translocation
Dendritic cells
Immunoglobins
Tolerance of Commensals
Th1
Treg
Nonspecific innate immune factors
B
Gut Epithelial Cells
Prebiotics
TLR4
PPARγ
PGJ2/PJ1
IL-10
IL-8
TNF-α
NF-κB
MIP2
MCP-1
GRO-α
IL-10
TNF-α
TGF-β
CXCR-8
Galectin-9
PKC
↓ inflammation
↓ acute allergic skin reaction
↓ mast cell degranulation
Skin barriers improvement
↓ bacterial infection
↑ Treg
C
Microbiota Fermentation
SCFAs
Prebiotics
Slc 16a1
Clc5a8
Passive diffusion
GPR41
GPR43
GPR109a
Olfr-78
Plasma membrane
MAPK
NFκB
HATs
HDACs
modulation of genes expression
nucleus
metabolism
cellular cycle
antimicrobial activity
D
Prebiotics
TLR4
PRR
Immune Cells
Monocyte
NF-κB
↑ IL-10
↑ IL-1
↑ TNF-α
B cell
T CD4+
IgA
↑ IL-10
IFN-γ
Treg
↑ Inflammation
↓ Inflammation


Control group
Standard cow's milk formula
Active group
Partially Hydrolyzed Protein Formula with Prebiotics
Reference group
Exclusively breastfed infants
Birth
4 weeks
Active group vs. Control group
↑ Bifidobacterium spp.
↓ Clostridium spp.
↓ Lachnospiraceae spp.
↓pH
↑ lactate (+ acetate)
↓ butyrate & propionate
↓ iso-butyrate & iso-valerate
12 weeks
cross feeding
Eubacterium spp.
Anaerostipes spp.
↓ butyrate
↑ butyrate
26 weeks
Eczema
No eczema
18 months



Milk replacer plus galacto-oligosaccharides significantly improved gut architectural features and villus/crypt ratio throughout the gastrointestinal tract, increased the number of goblet cells and revealed a differential abundance of beneficial probiotic bacteria, particularly Lactobacillus and Bifidobacterium.

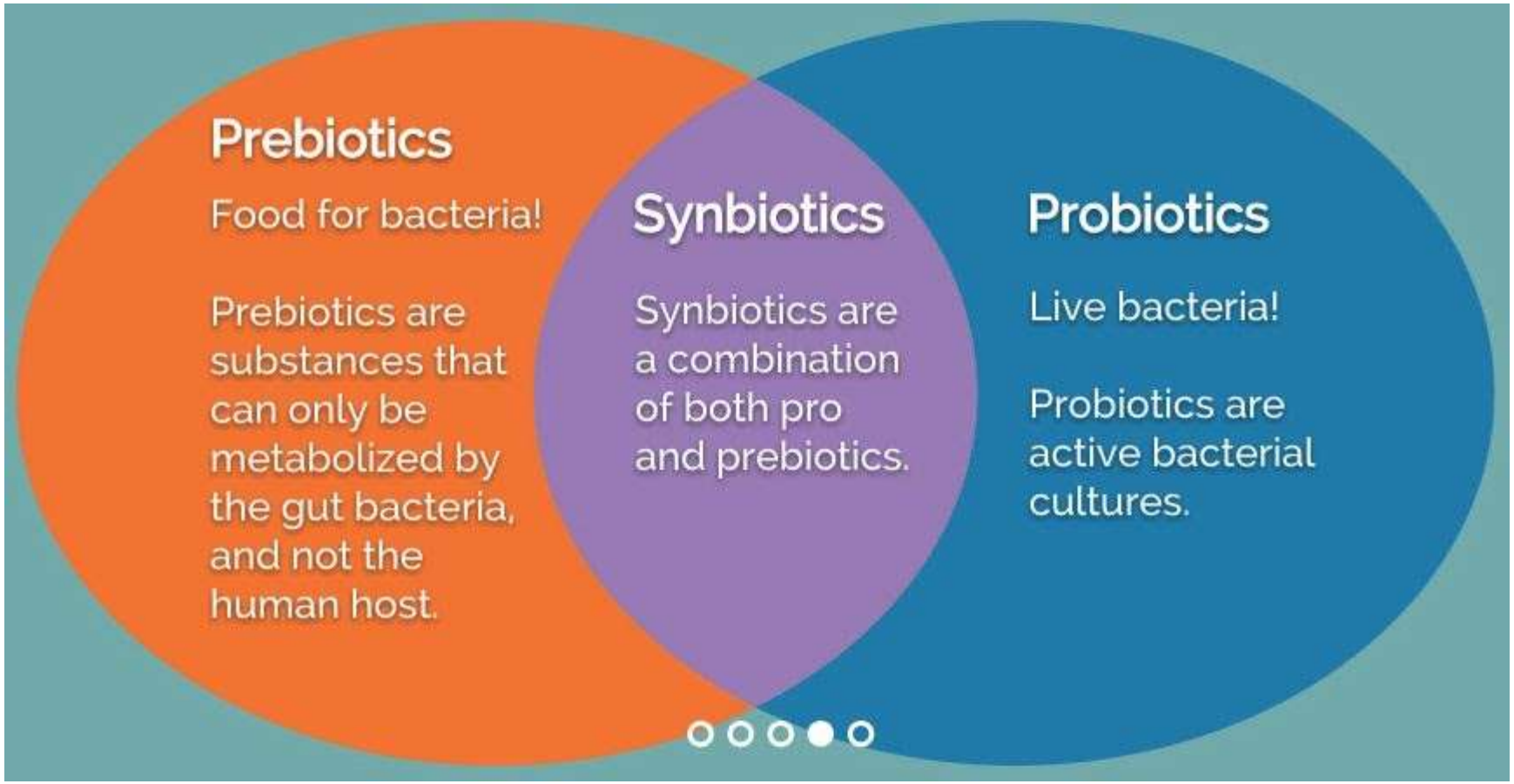


Source: https://www.frontiersin.org/articles/10.3389/fphar.2021.712531/full

At this time, on the basis of currently available data, supplementation with probiotics for prevention of allergies in children cannot be recommended, even if it is possible to underline the net benefit in high-risk infants in the prevention of eczema, as this effect is predominantly constant across studies available in the literature. However, the optimal strains, dose and timing, and duration of supplementation are still unknown, although a combined pre- and post-natal intervention appeared of stronger benefit. Moreover, the evidence for recommendation of prebiotic supplementation in infants who are not exclusively breastfed is of very low certainty and quality. Therefore, conclusive evidence is still lacking to be able to recommend routine use of pre/probiotics for allergic preventive purposes.

The bifidogenic effect of human milk (rich in oligosaccharides) is well-known. Prebiotics have long been added to infant milk formulas to mimic these functional characteristics of breast milk (52, 80, 81). A combination of galacto-oligosaccharide (GOS) and fructo-oligosaccharide (FOS) (scGOS 90% plus lcFOS 10%) was prebiotic of choice in a number of intervention trials. Acidic oligosaccharides (AOS), polydextrose (PDX) (with or without lactulose), different content of lactose, oligofructose plus inulin have also been tested (Table 1). Modification of intestinal microbiota represents the principal way by which this effect has been orchestrated (93) and has been reported in several studies (82, 90, 92, 94, 95). The 2'-fucosyllactose (2'-FL) human milk oligosaccharide (HMO), the most plentiful HMO in most human milk, has been recently synthesized and is now commercially available in few supplemented infant formulas, bringing the composition closer to human milk (95).

Synbiotics

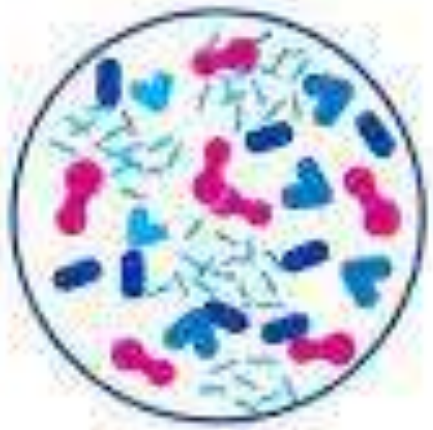

Prebiotics
Food for bacteria!
Prebiotics are substances that can only be metabolized by the gut bacteria, and not the human host.
Synbiotics
Synbiotics are a combination of both pro and prebiotics.
Probiotics
Live bacteria!
Probiotics are active bacterial cultures.

Probiotics

Prebiotics

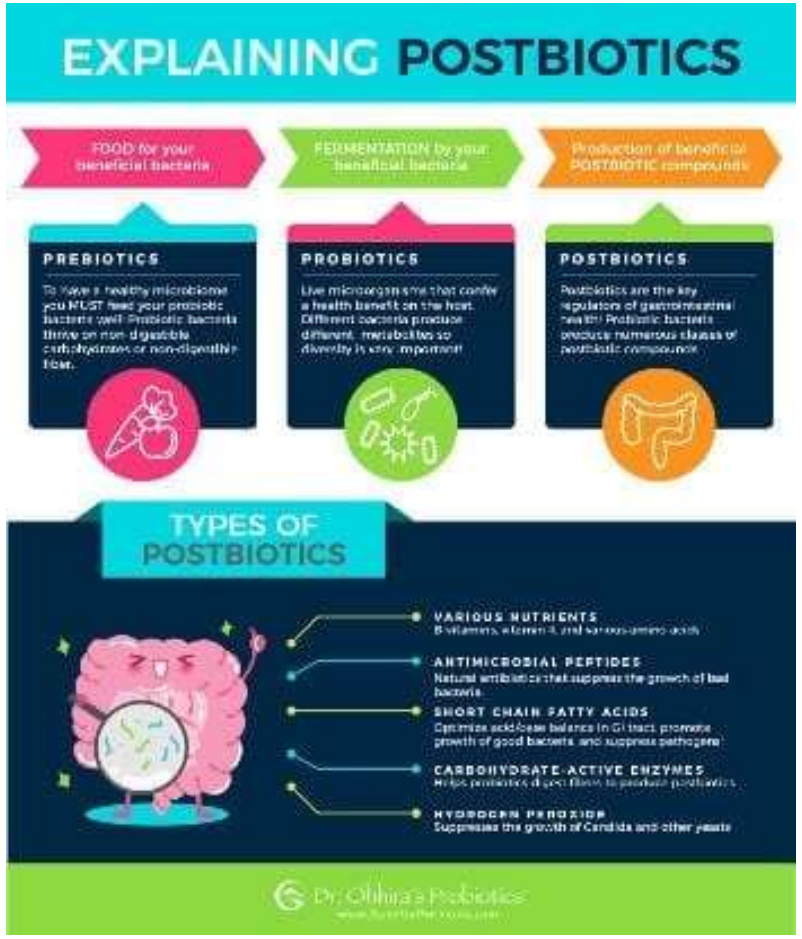
Synbiotics

Combination of both probiotics and prebiotics



Postbiotics

Postbiotics



- **Bacteriocins** *(protective compounds that make life hard for the bad guys)**
- **Enzymes** *(help to digest food, get rid of toxins and assist other metabolic processes)**
- **Vitamins** *(like the B's and vitamin K)**
- **Amino acids** *(building blocks of protein)**
- **Neurotransmitters** *(carry messages between the nerves and brain and can even affect appetite)**
- **Immune-signaling compounds** *(they support the body's immune cells)**
- **Short-chain fatty acids** *(created from fiber, they keep the intestinal lining strong and healthy)**
- **Nitric oxide** *(crucial for cardiovascular health)**
- **Organic acids** *(such as Fulvic and Humic acid. They combine with minerals, making them easier to absorb and help maintain the correct pH in the GI tract)**

Postbiotic concepts

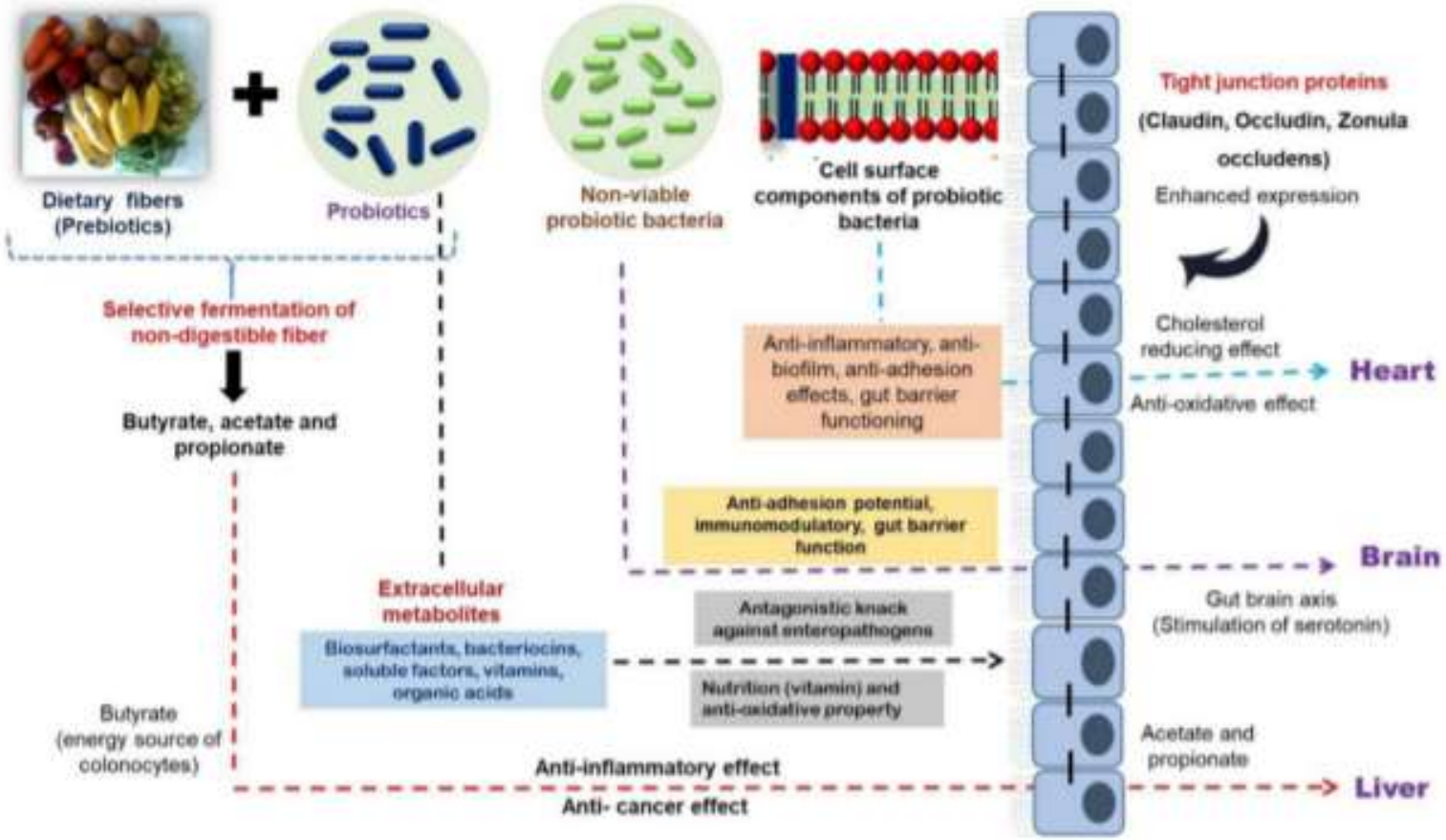
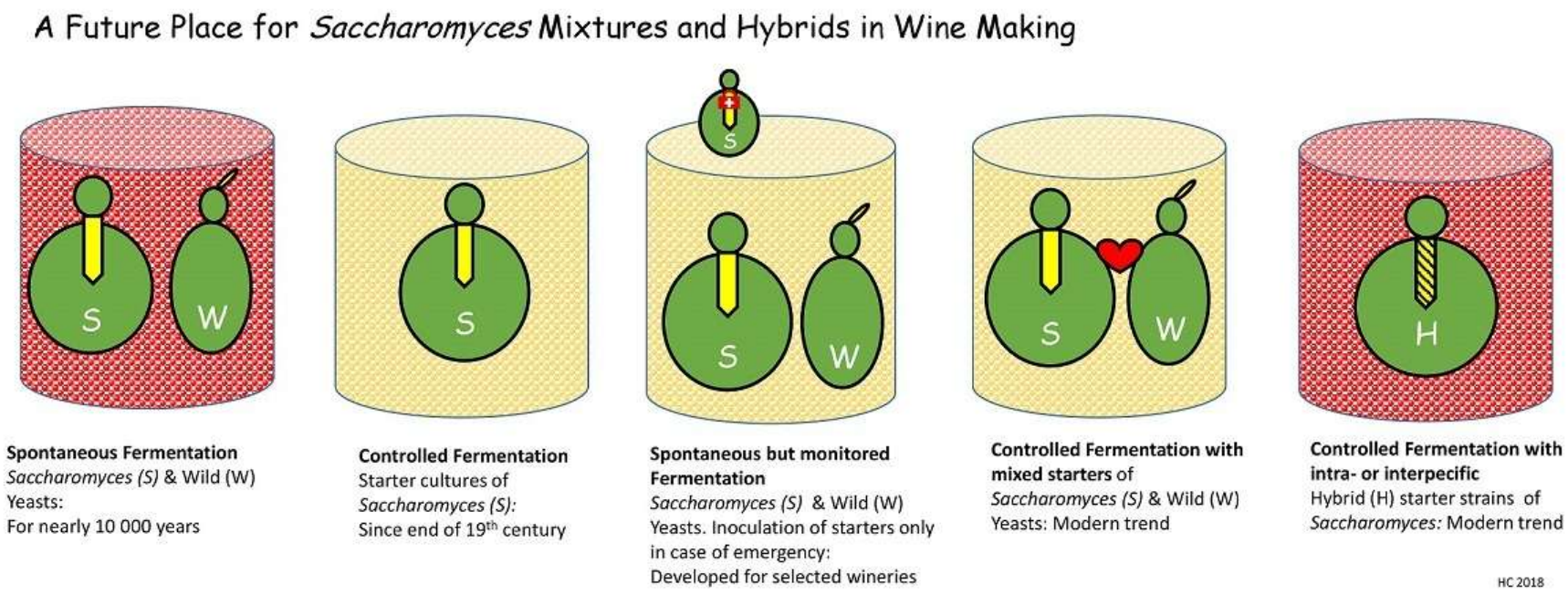
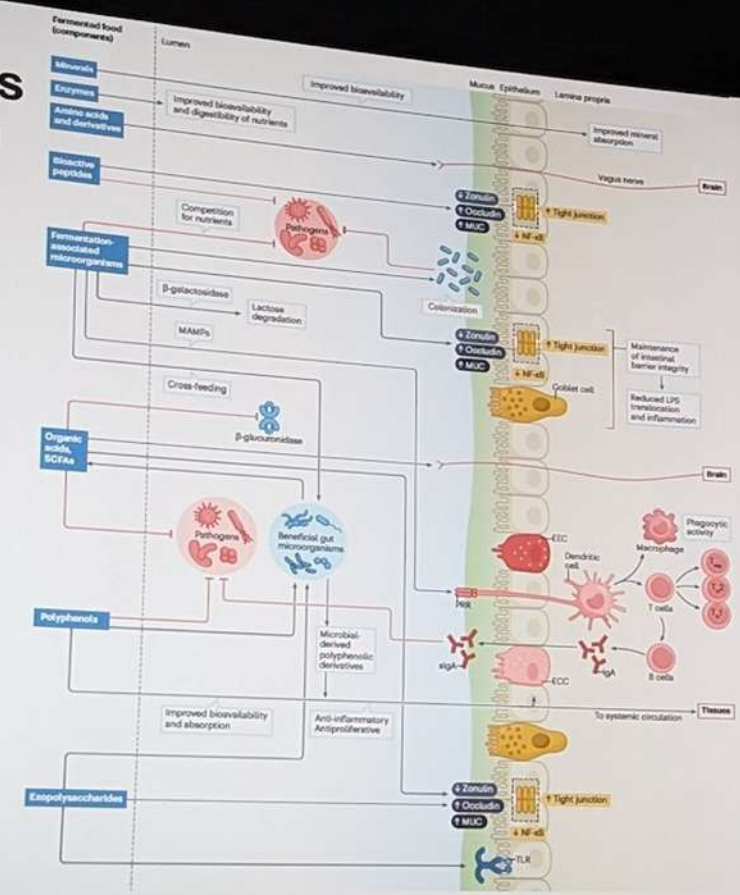


Figure 18. Schematic representation of various health benefits of postbiotic molecules [165]

Fermentation spontaneous stater cultures



Health benefits (mechanisms)

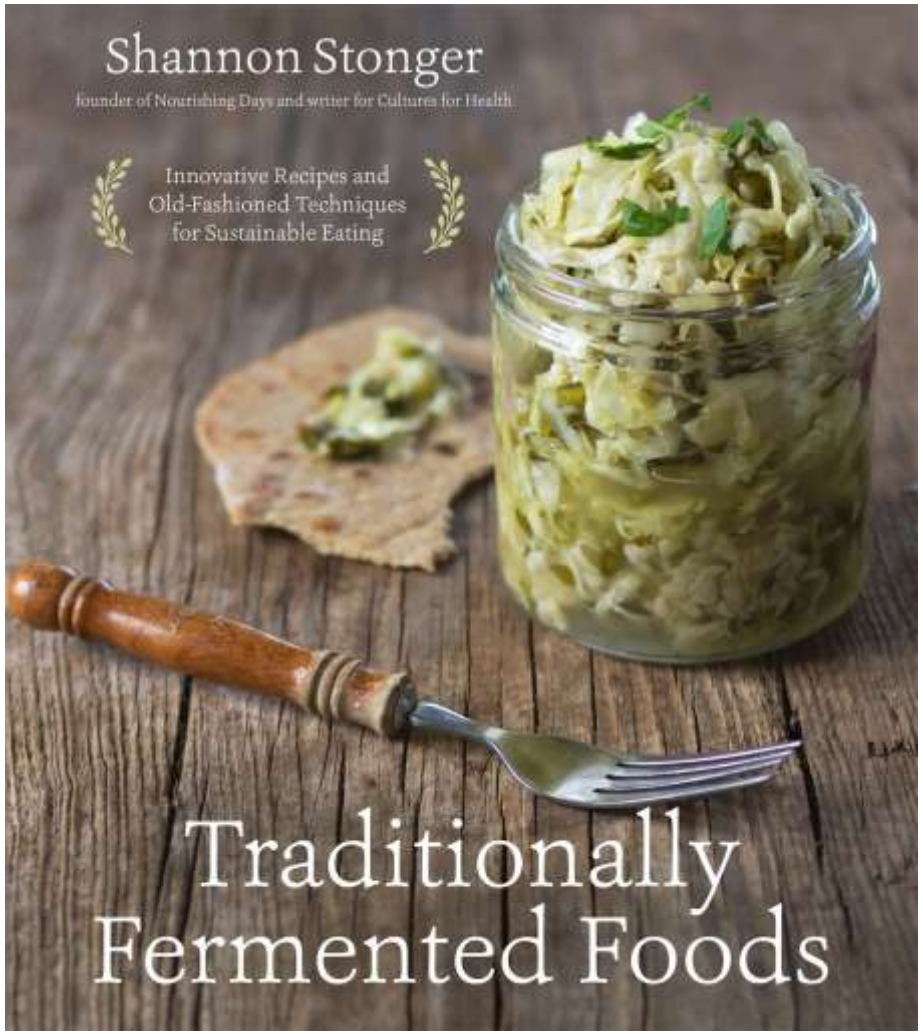


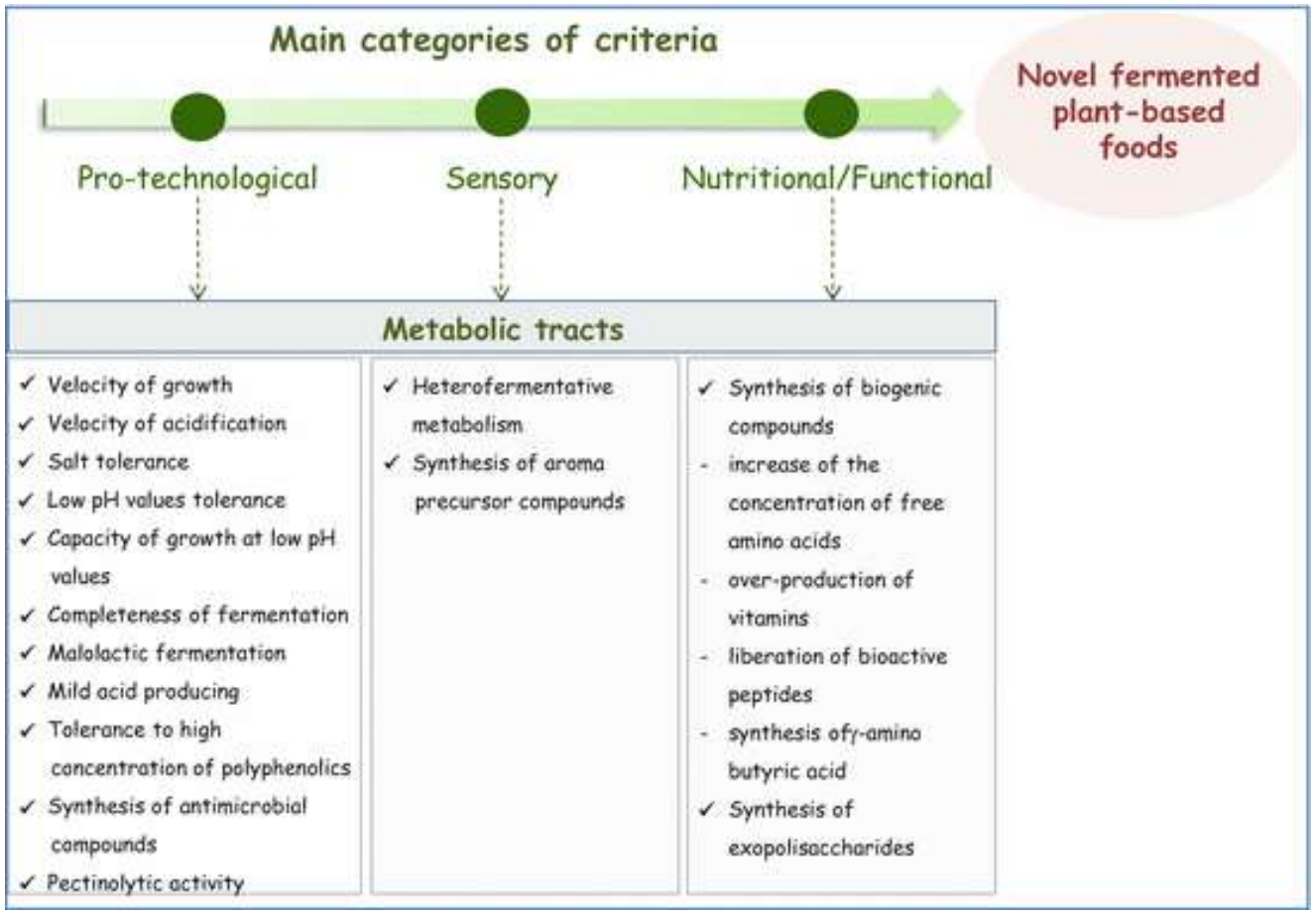
Fermentation can also remove of undesirable compounds from substrates

Mycotoxins
Lactose
FODMAPs
Gluten
Trypsin Inhibitors (plants, especially legumes)
Phytic acid (cereals, legumes, seeds)
Vicine and convicine (glucosides; faba bean)
Cyanogenic glycosides (bitter cassava)

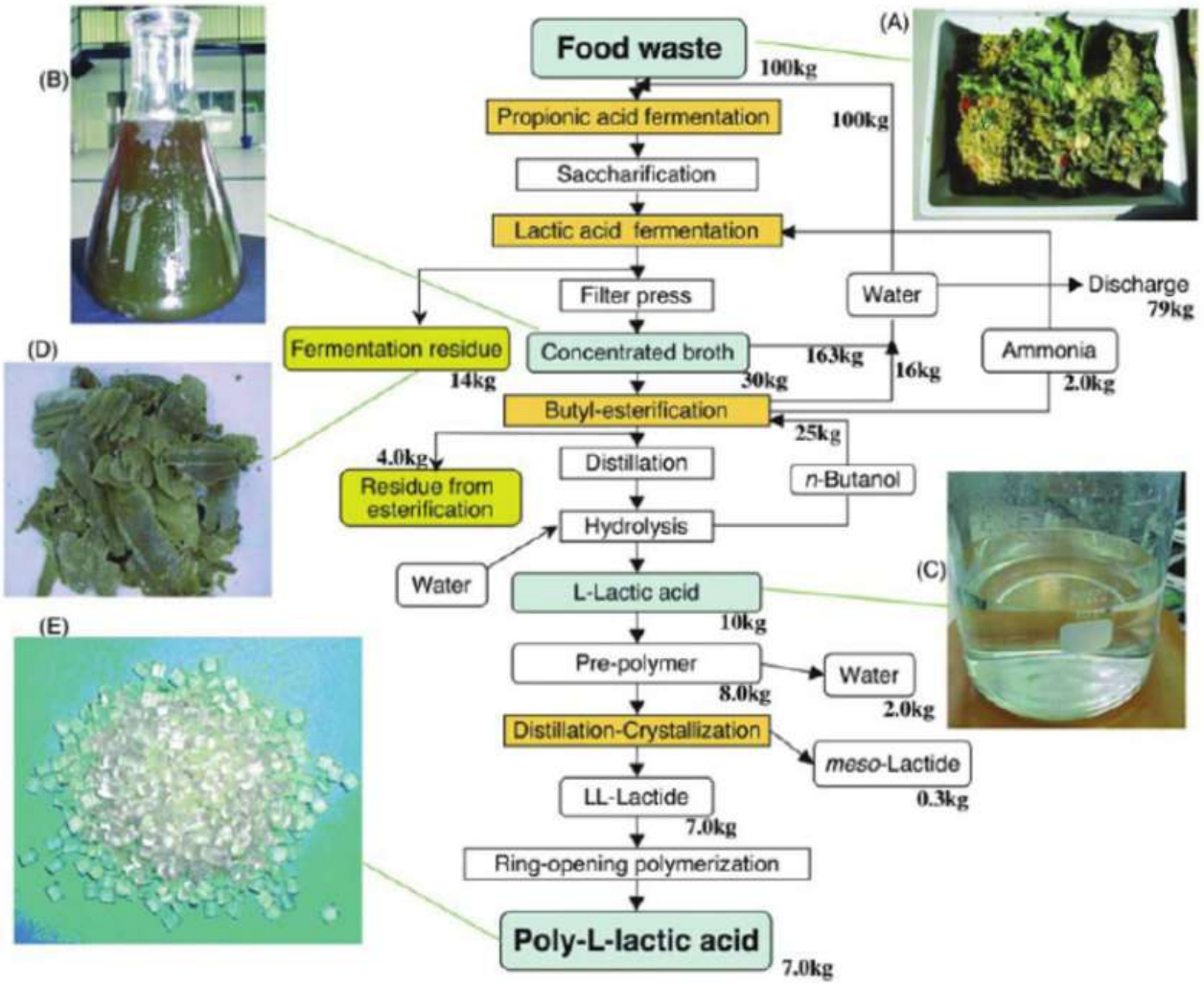
Mukherjee et al 2024 Nat Rev Gastro Enterol

Fermentation between tradition and novel possibilities





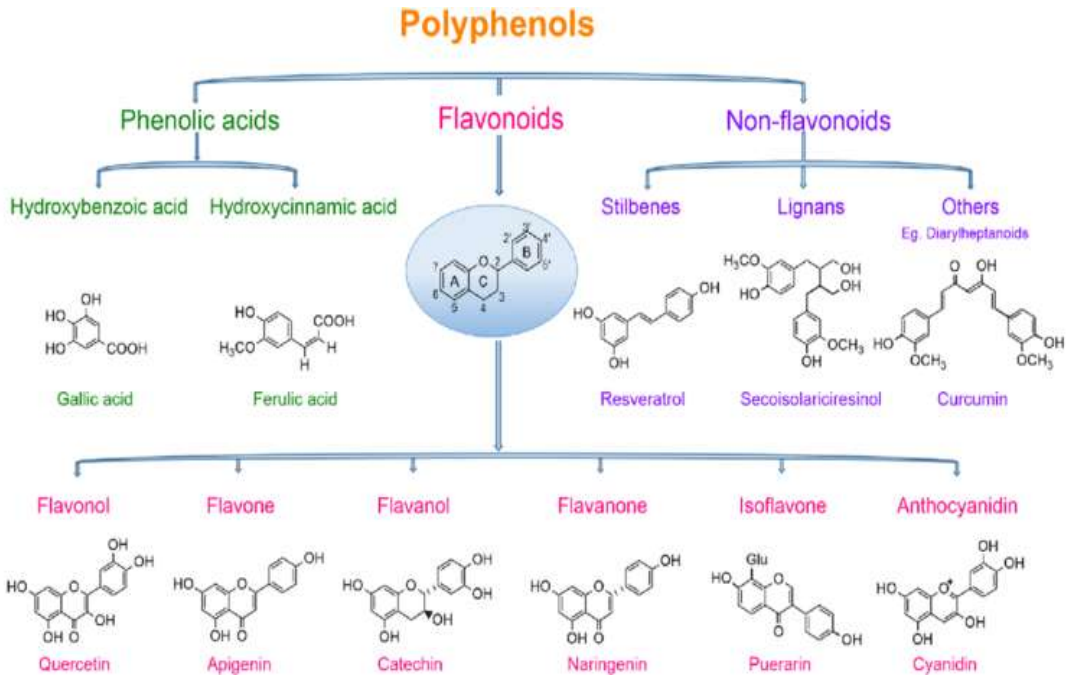
Fermentation of food waste results in usefull molecules



Bioactive plant ingredients, fuctional foods, sekundaere Pflanzeninhaltsstoffe

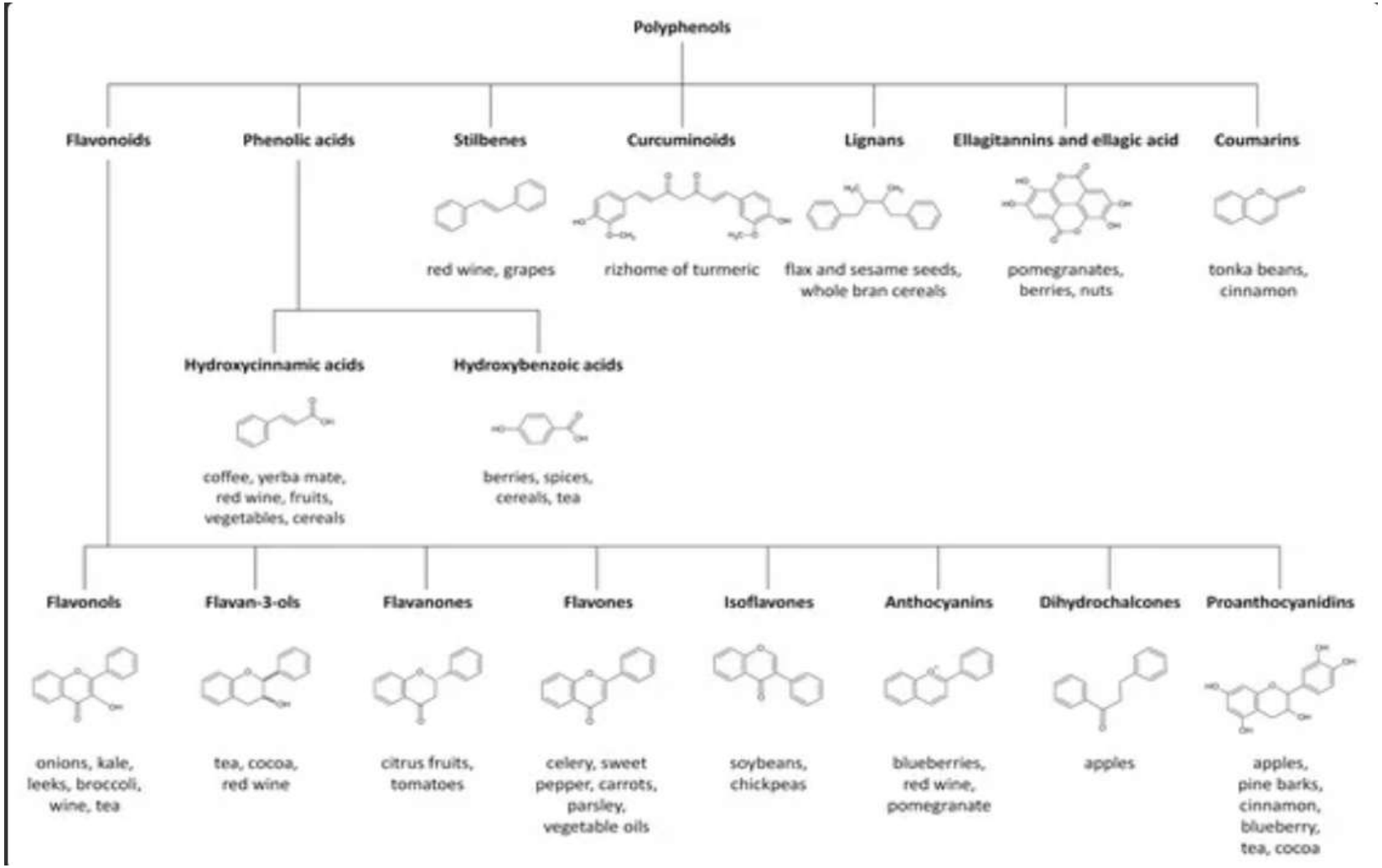
Gruppe	Grundbausteine	Substanzklasse
Phenolische Verbindungen	Shikimat Phenylalanin Phenylalanin + Polyketid	Polyphenole einfache Phenole Phenylpropan-Derivate Flavonoide Stilbene
Isoprenoide Verbindungen	„aktives Isopren" (C_5)	Hemiterpene (C_5) Monoterpene (C_{10}) Sesquiterpene (C_{15}) Diterpene (C_{20}) Triterpene (C_{30}) Tetraterpene (C_{40}) Polyterpene
Pseudoalkaloide	Terpenoide, Polyketid	Terpenoid-Alkaloide einige Piperidin-Alkaloide
„echte" Alkaloide	Aspartat Lysin Ornithin, Arginin Tyrosin Tryptophan Glycin	Tabak-Alkaloide Lupinen-Alkaloide Pyrrolizidin-Alkaloide Tropan-Alkaloide Benzylisochinolin-Alkaloide Indol-Alkaloide Purin-Alkaloide

Polyphenols

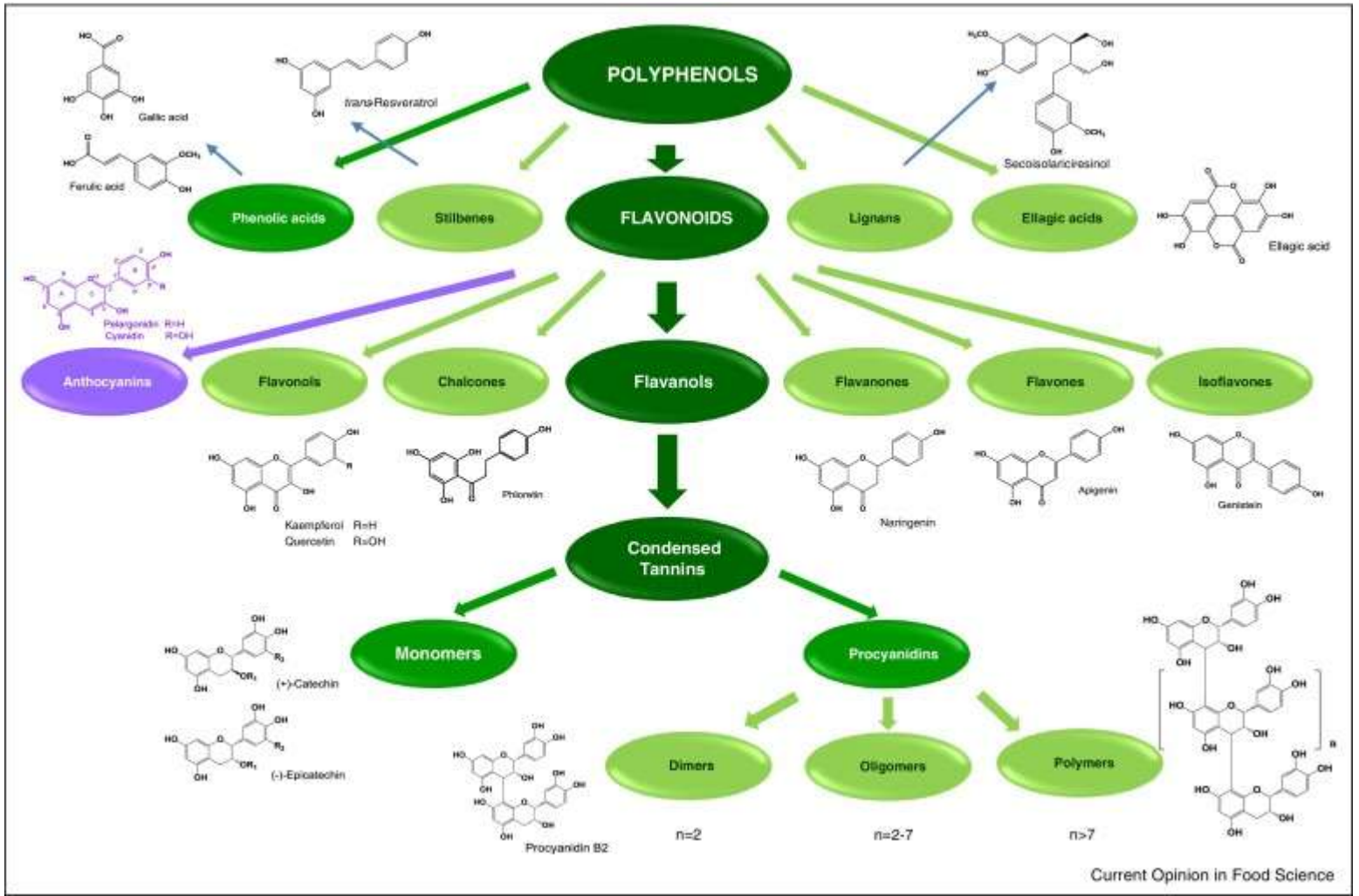


Polyphenols are molecules chemically characterized by the presence of at least one aromatic ring with one or more hydroxyl groups attached . Polyphenols are plant secondary metabolites that are thought to help plants to survive and proliferate, protecting them against microbial infections or herbivorous animals, or luring pollinators . Polyphenols are found in many medicinal and edible plants which represent important alimentary sources, including fruits, vegetables, beverages (such as tea and red wine) and extra virgin oil

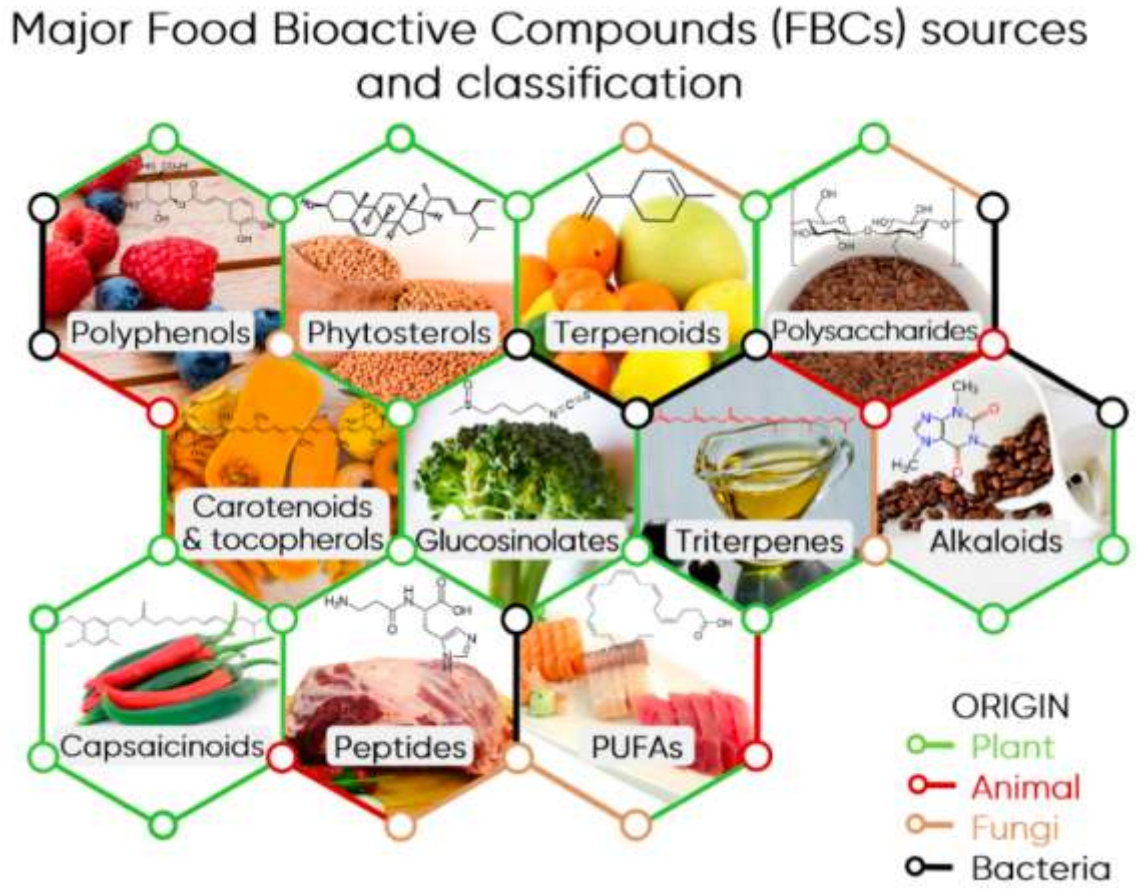
Polyphenols and their plant sources,

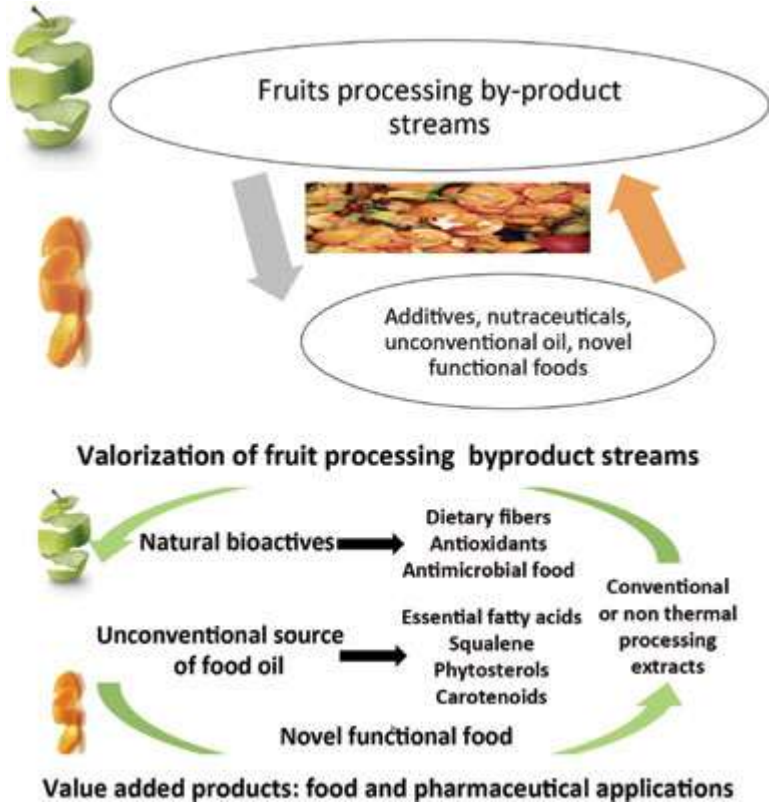


Anthocyans

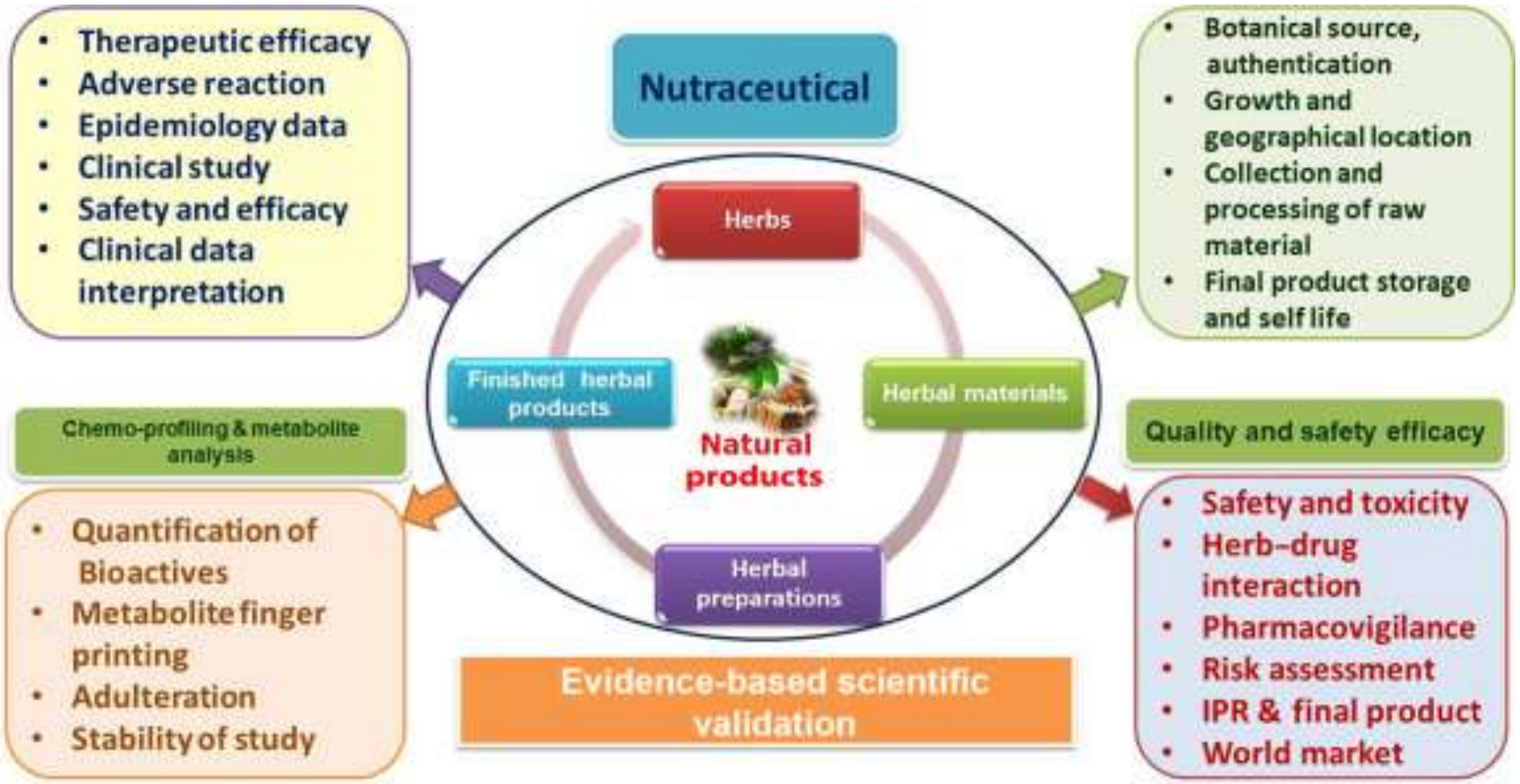

POLYPHENOLS
Gallic acid
trans-Resveratrol
Ferulic acid
Secoisolariciresinol
Phenolic acids
Stilbenes
FLAVONOIDS
Lignans
Ellagic acids
Ellagic acid
Pelargonidin R=H
Cyanidin R=OH
Anthocyanins
Flavonols
Chalcones
Flavanols
Flavanones
Flavones
Isoflavones
Kaempferol R=H
Quercetin R=OH
Phloretin
Naringenin
Apigenin
Genistein
Condensed Tannins
Monomers
Procyanidins
(+)-Catechin
(-)-Epicatechin
Procyanidin B2
Dimers
Oligomers
Polymers
n=2
n=2-7
n>7
Current Opinion in Food Science

Types and classification of bioactive compounds from food

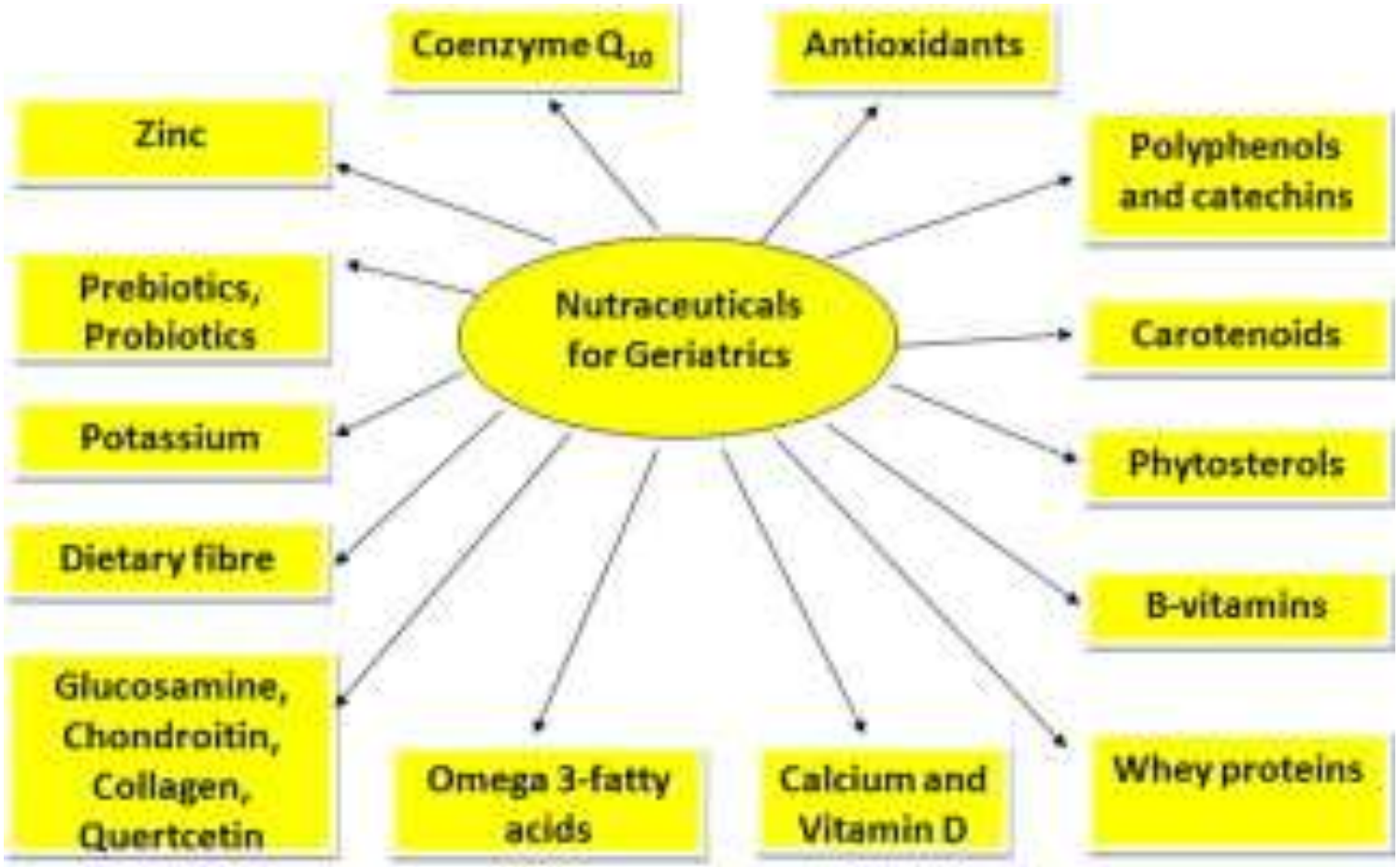




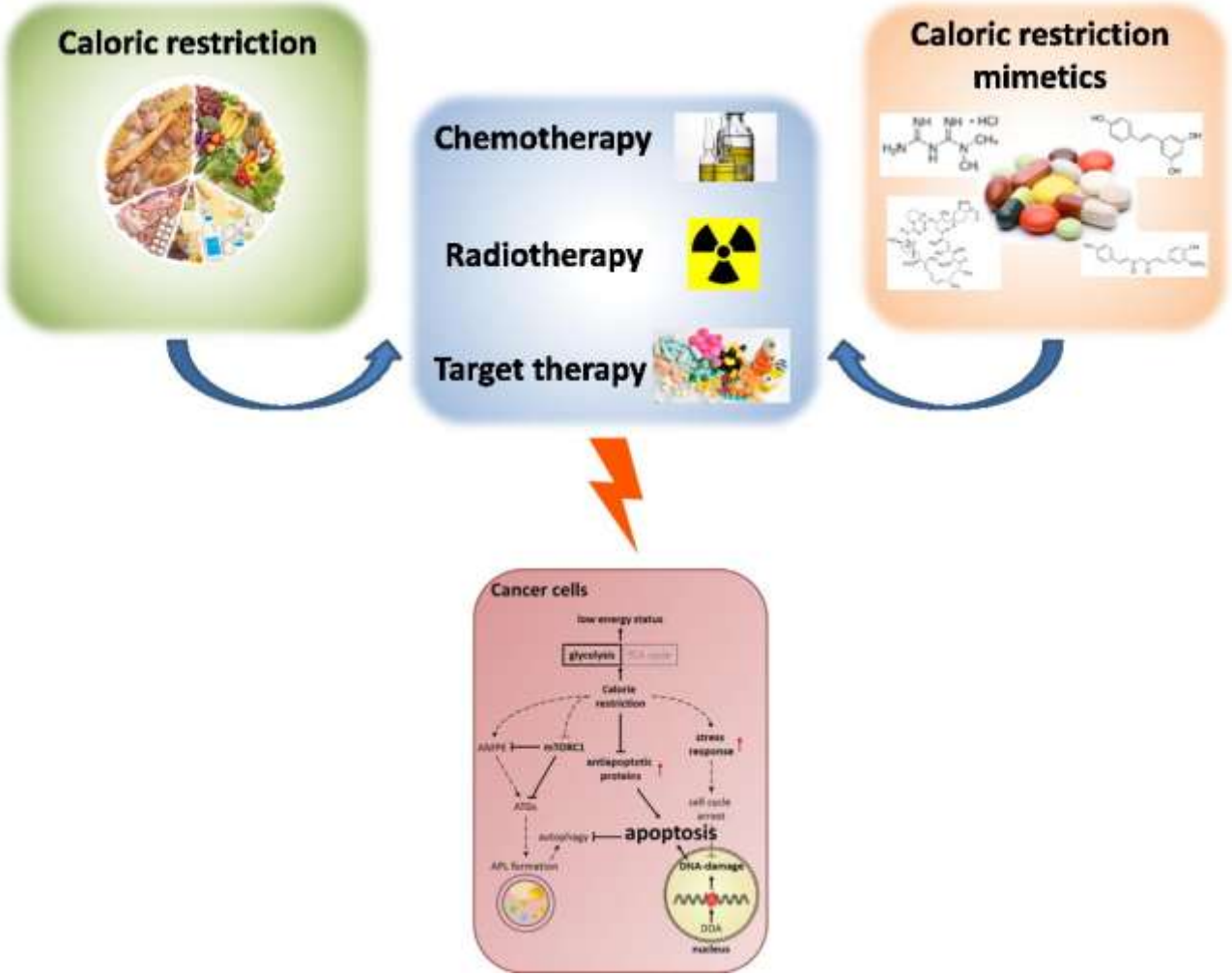
Nutraceuticals



Nutraceuticals for aging



The best nutraceutical for healthy aging:CR fasting, taken as an example for desired activities

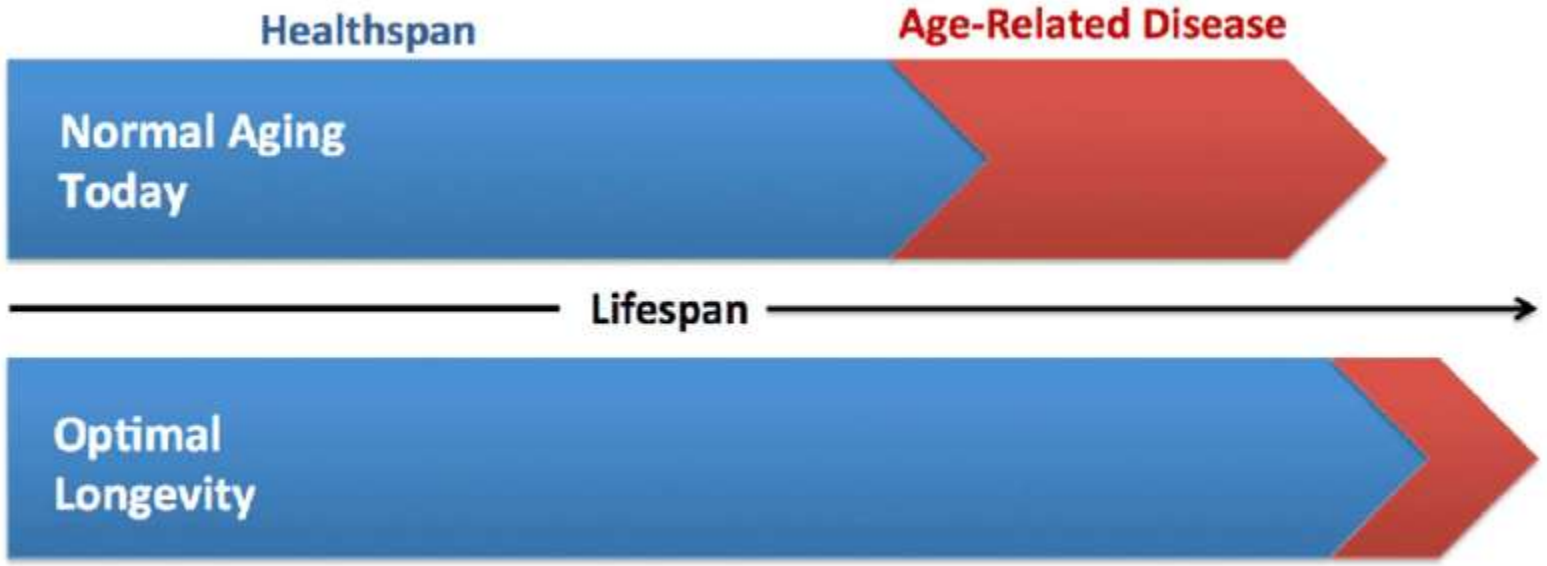


Fasting

- abstain from all/or some kinds of food or drink for a defined time. Has been implicated in religious cultures through out the world
- Voluntary in contrast to starvation,
- Hippocrates (460- 370 v.Chr) und Hildegard von Bingen (1098-1179)
- 20th century: Dr. Buchinger (Witzenhausen 1878-1966),
- CR: fasting, intermitted fasting, alternative day fasting.. without malnutrition

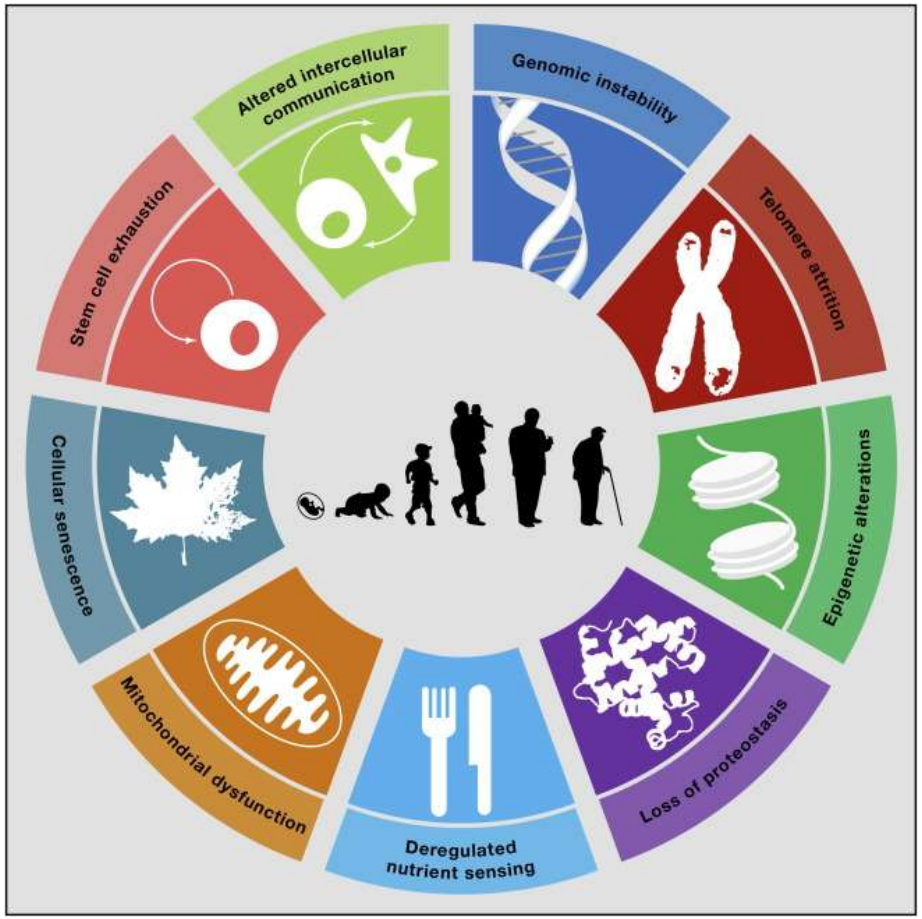
R. Mesnage, F. Grundler, A. Schwiertz, Y. Le Maho, and F. Wilhelmi de Toledo, “Changes in human gut microbiota composition are linked to the energy metabolic switch during 10 d of Buchinger fasting,” *J. Nutr. Sci.*, vol. 8, p. e36, 2019, doi: 10.1017/jns.2019.33.

So, can we increase health span by fasting, CR ?



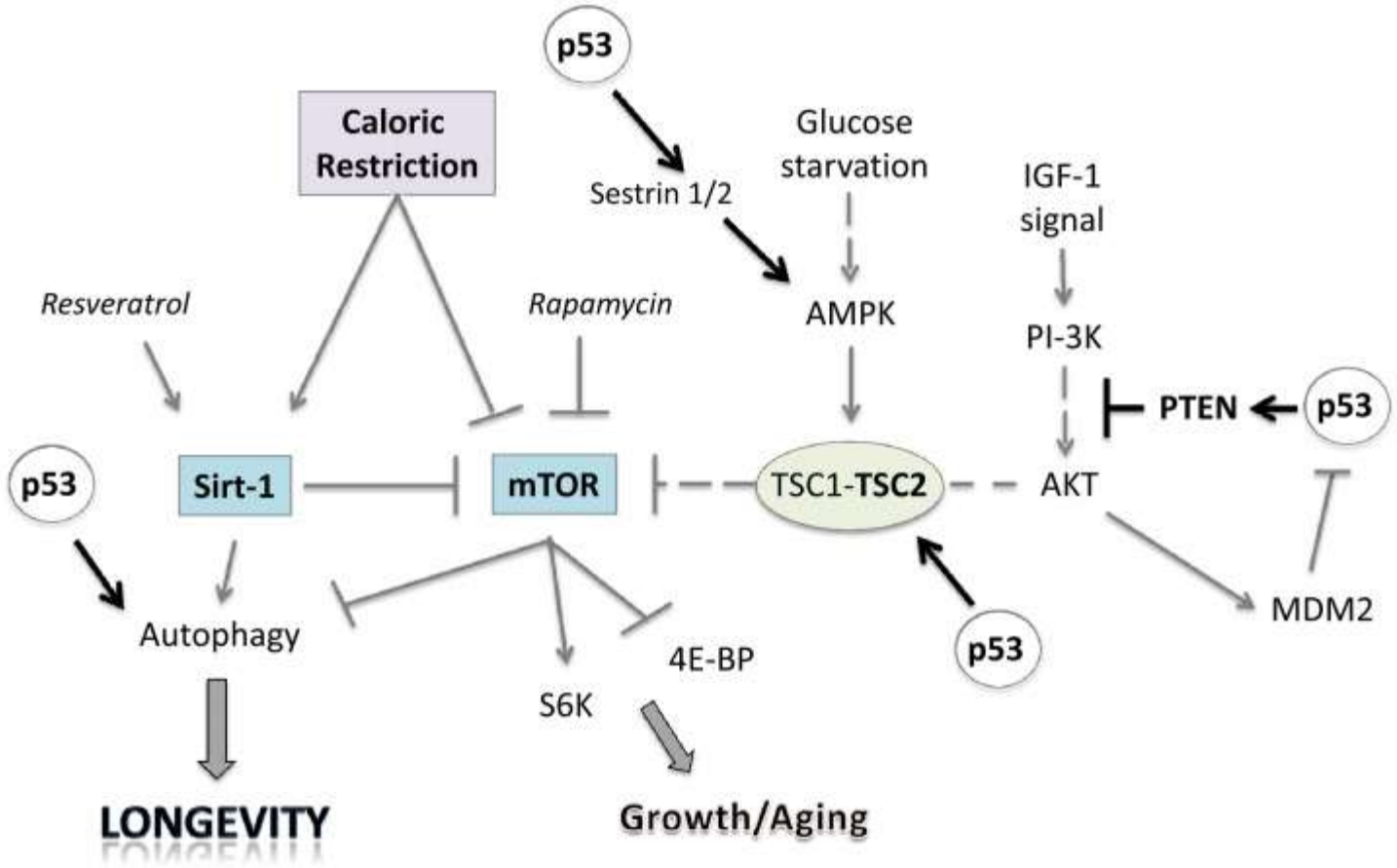
So what contributes to age related diseases/premature aging

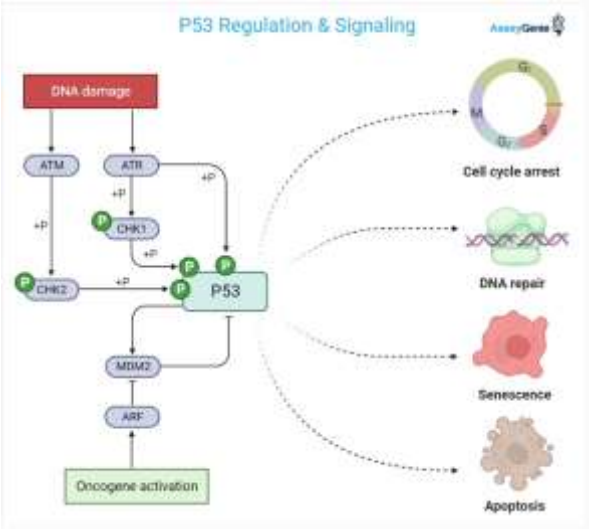
Aging/ health are defined by its hallmarks

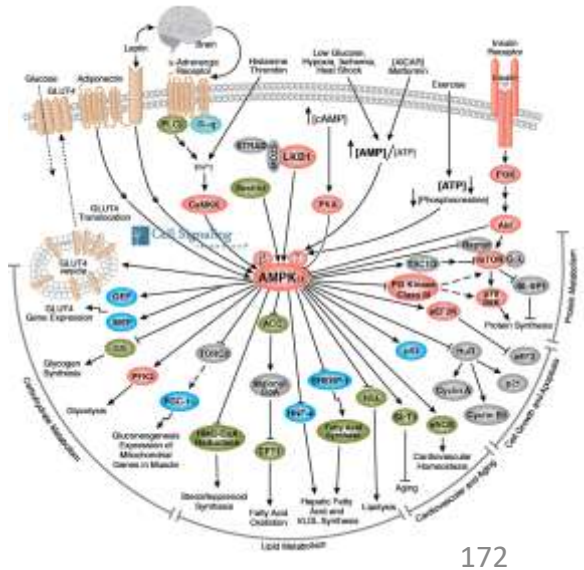


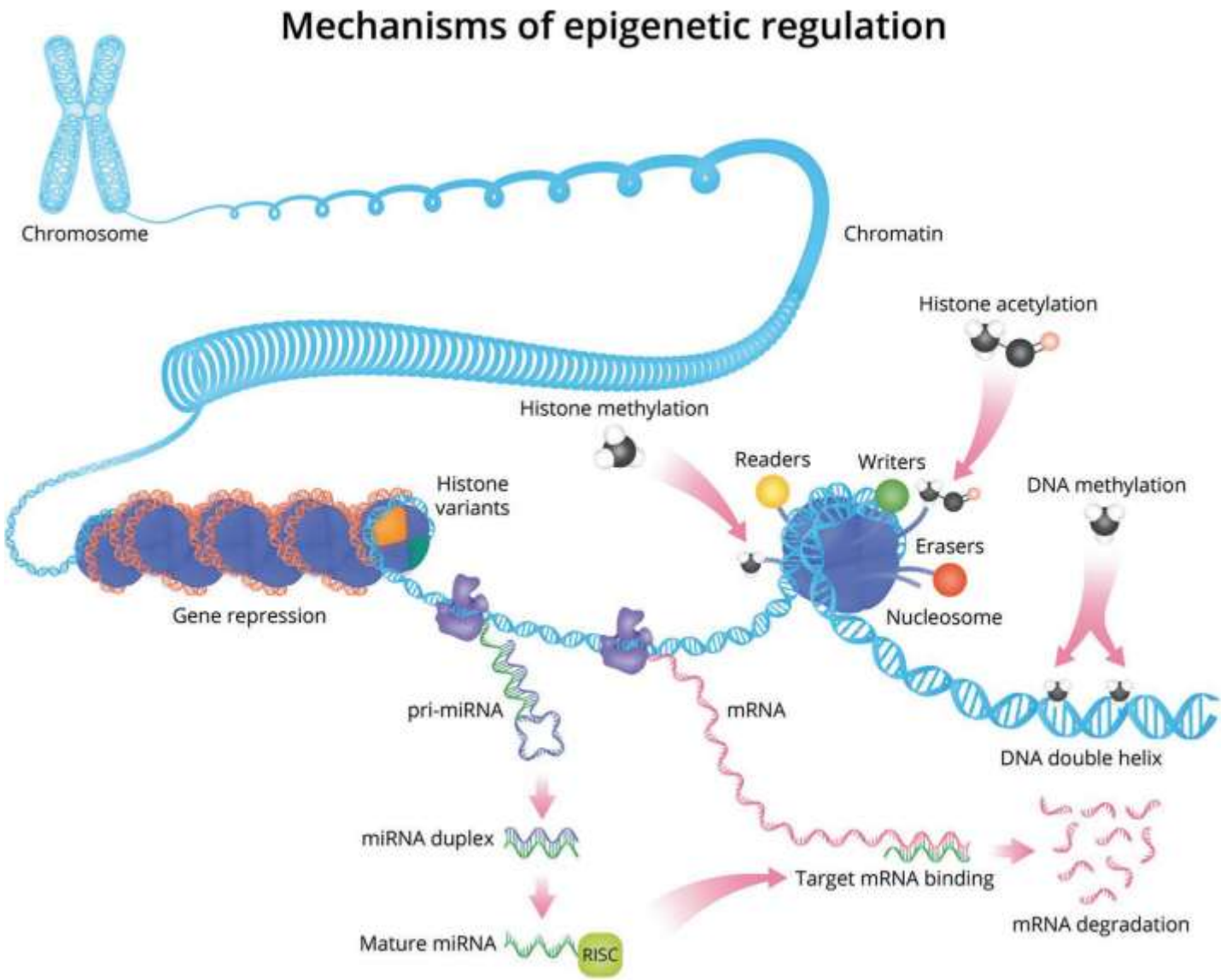
C. López-otín, M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer, "The Hallmarks of Aging Longevity," *Cell*, vol. 153, no. 6, pp. 1194–1217, 2013, doi: 10.1016/j.cell.2013.05.039.The.

Fasting mechanisms: AMPK, SIRT, mTOR, p53





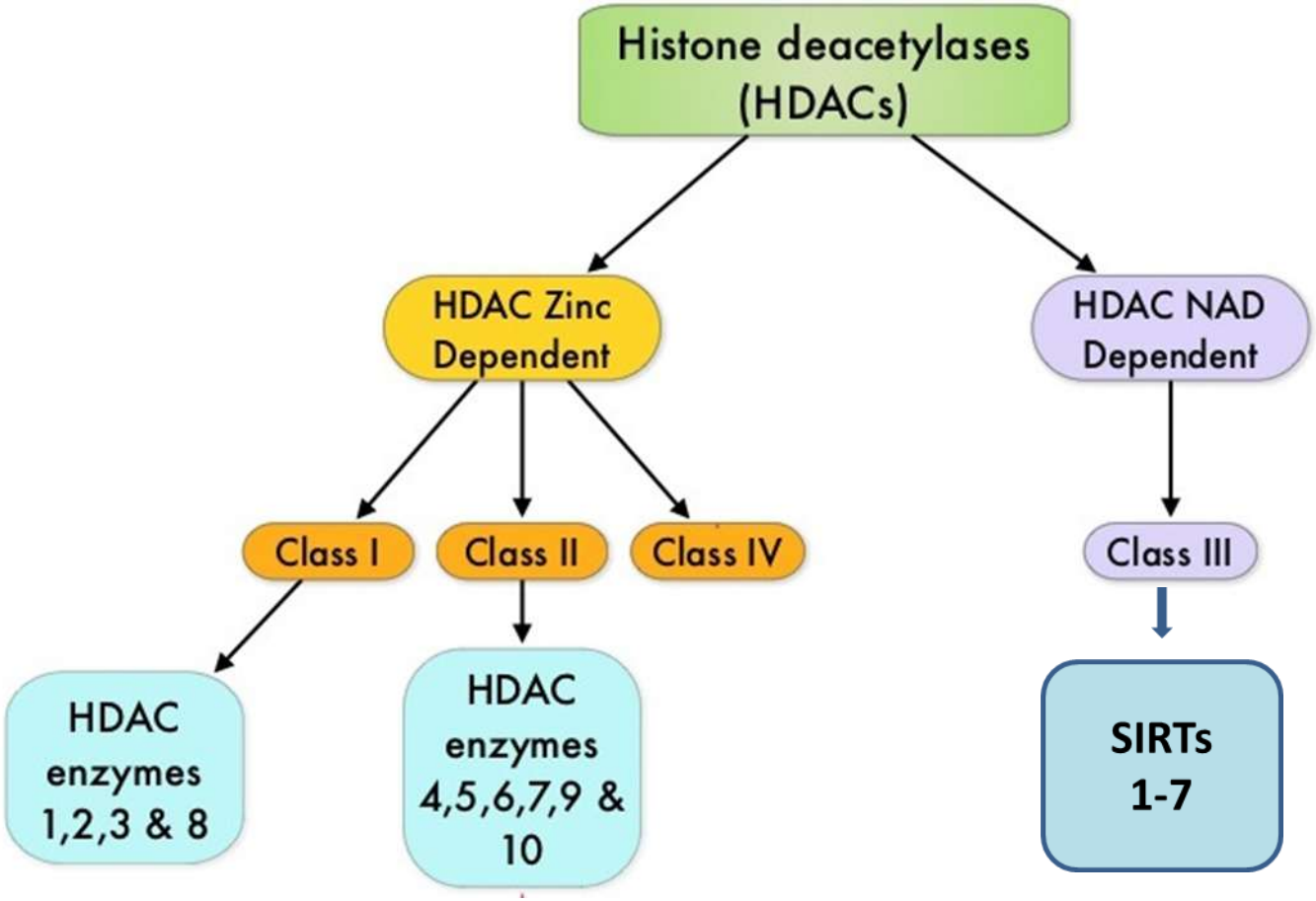


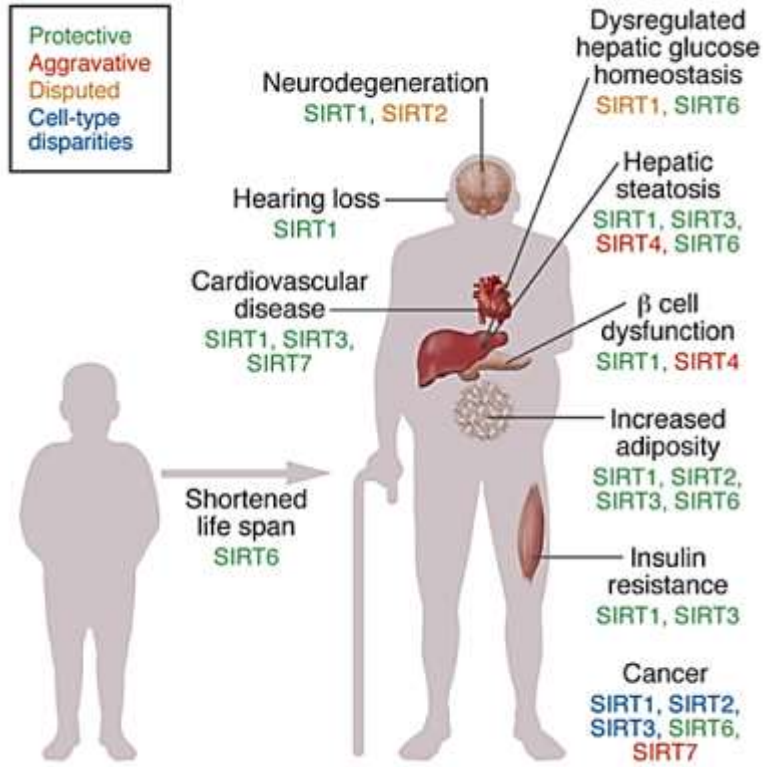


- The “above genetic”
- Impacts transcription without changing the sequence of the DNA
- originally developed as a host defense and protection of the genome stability
- silencing or activate gene expression
- Can be influenced
- Alterations have been associated with different pathologies

L. Smigielski, V. Jagannath, W. Rössler, S. Walitza, and E. Grünblatt, “Epigenetic mechanisms in schizophrenia and other psychotic disorders: a systematic review of empirical human findings,” *Mol. Psychiatry*, vol. 25, no. 8, pp. 1718–1748, 2020, doi: 10.1038/s41380-019-0601-3.

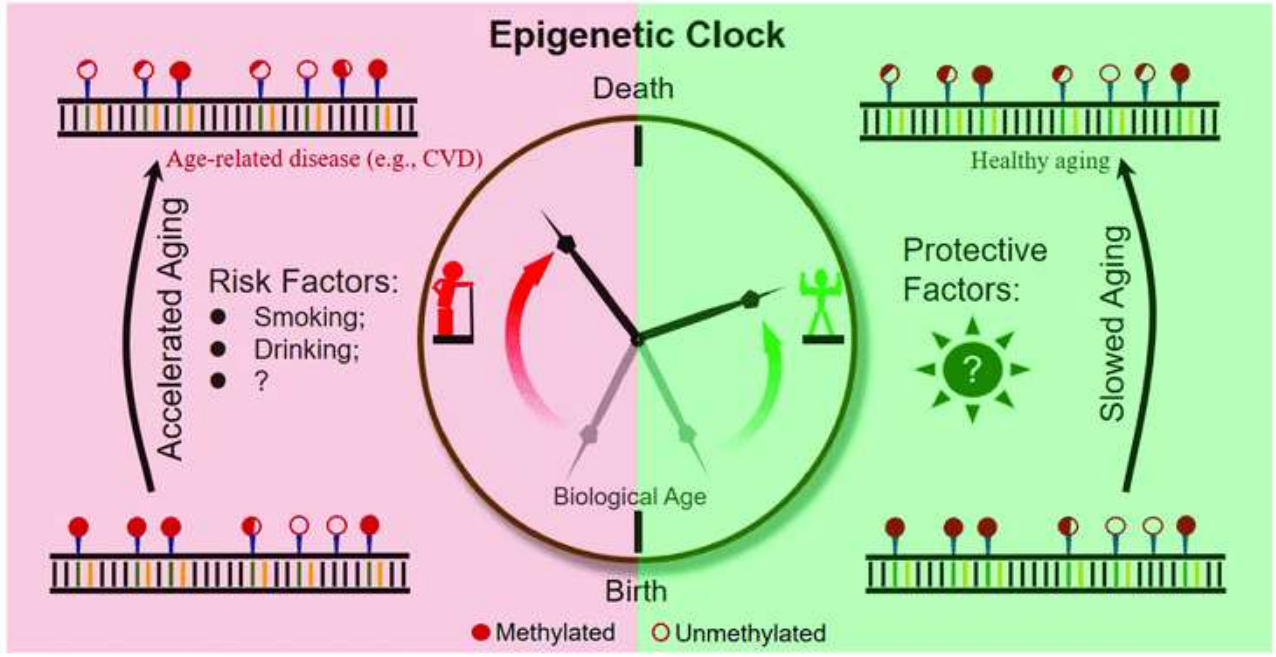
Histone deacetylases, Sirtuins

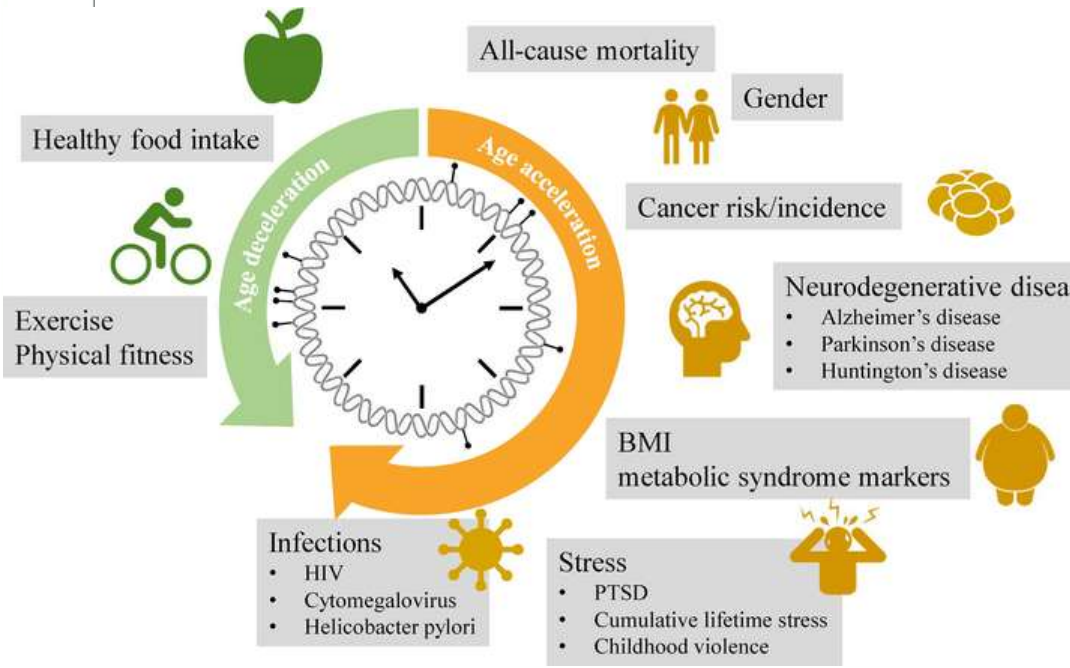




J. A. Hall, J. E. Dominy, Y. Lee, and P. Puigserver, "The sirtuin family's role in aging and age-associated pathologies," *J. Clin. Invest.*, vol. 123, no. 3, pp. 973–979, 2013, doi: 10.1172/JCI64094.

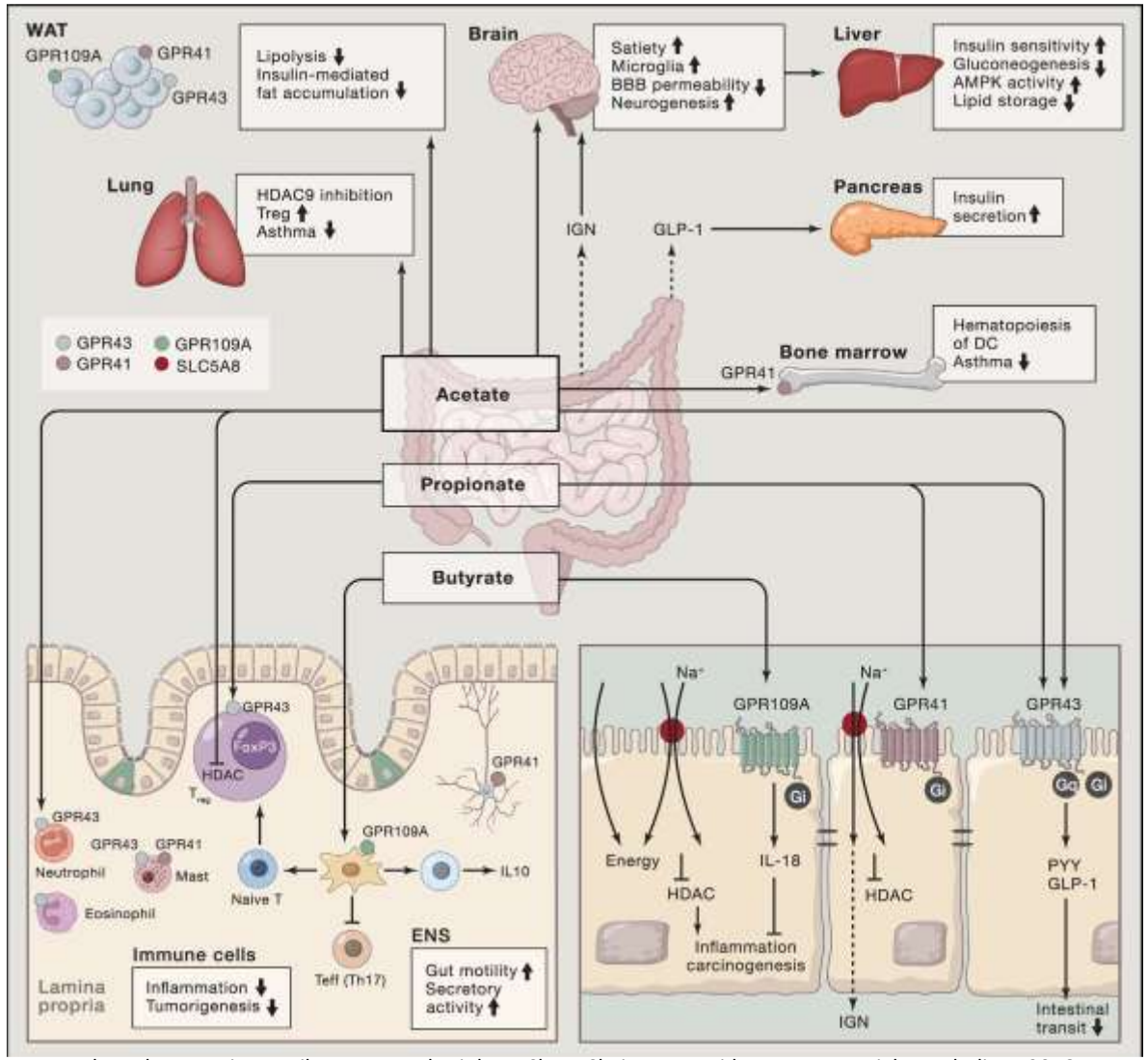
Epigenetic clock





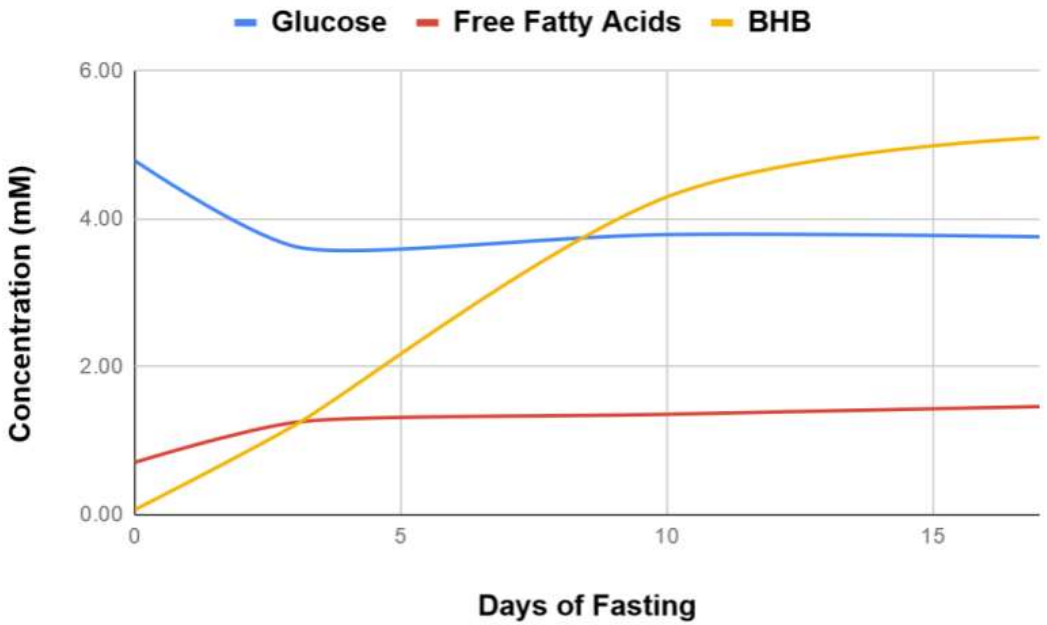
The gut microbiome and SCFAs

- not defined as a hallmark of aging, causal relationships have been observed between the microbiome and age
- *Firmicutes, Bacteroidetes and Actinobacteria*
- Inter-individual changes are determined by genetic, age, diet, health and geographic origin
- Composition and diversity declining with age
- Epigenetically active metabolites – SCFAs
  - Target HDACs, GPCRs, used for energy production
  - declines with aging
- Decline leads to obesity, inflammation, insulin resistance with further DM2, cardiovascular disease, neurological disorders…



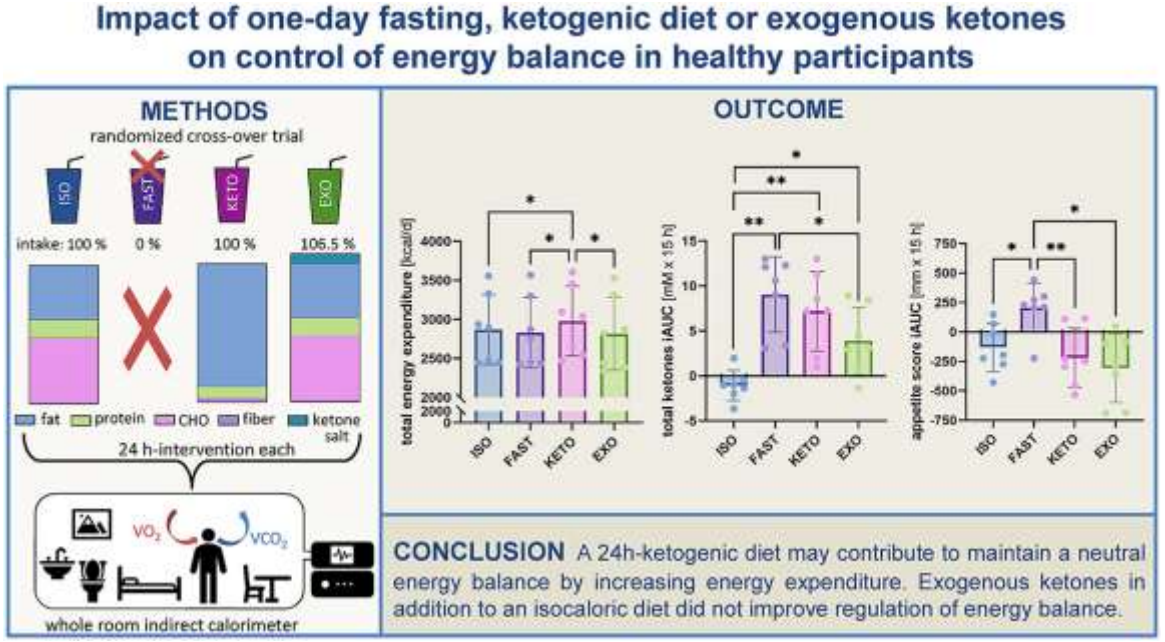
Koh et al. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites, 2016

CR, Fasting, Intervallfasten 18/6, ketogenesis



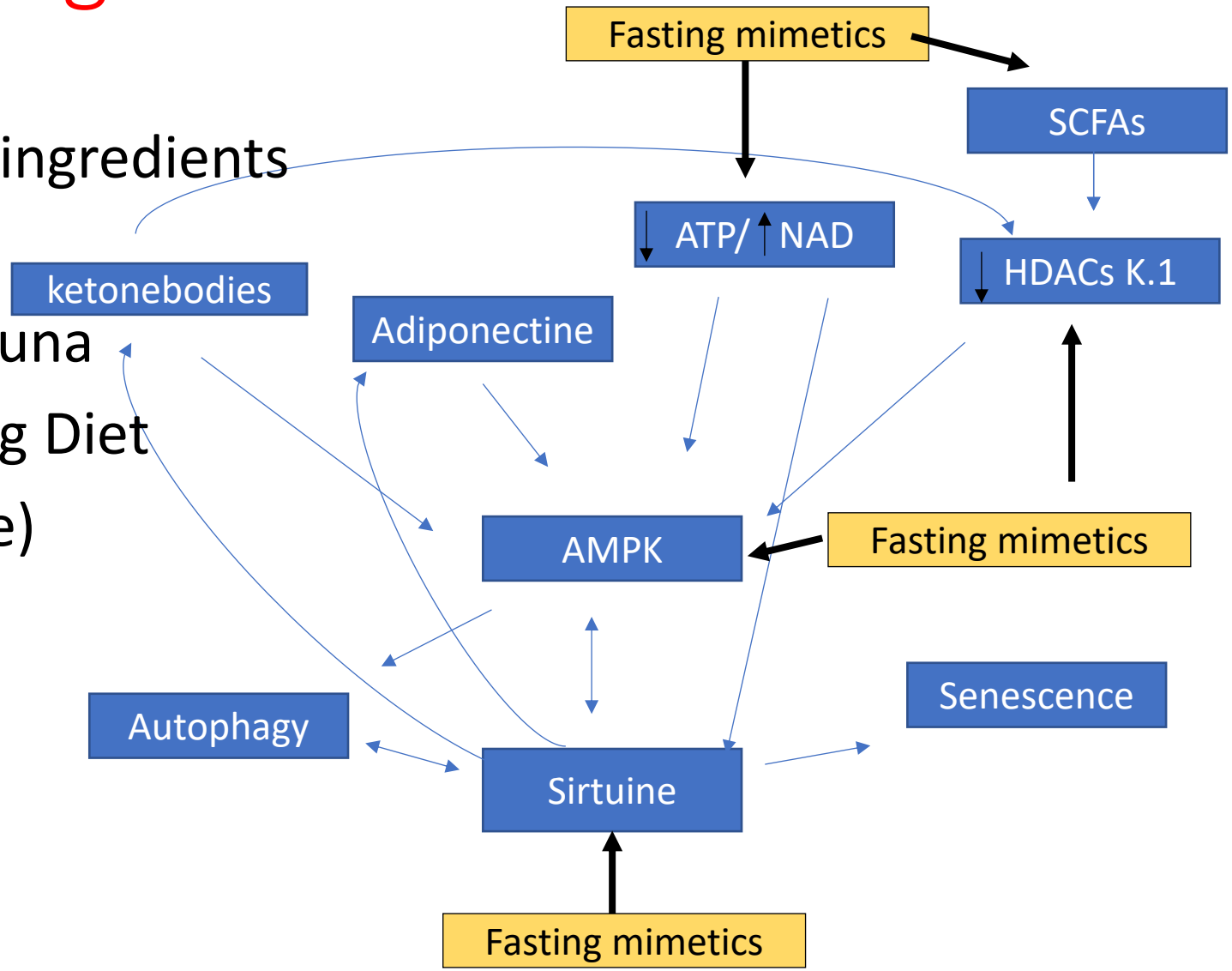
Source: Owen, O. E., Felig, P., Morgan, A. P., Wahren, J. & Cahill, G. F., Jr. Liver and kidney metabolism during prolonged starvation. *J Clin Invest* **48**, 574-583, doi:10.1172/JCI106016 (1969).

Ketosource®



Fasting or Fasting mimetics?

- Secondary plant ingredients
- Ketogenic diet
- Cold therapy/ Sauna
- Fasting mimicking Diet
- Sport (endurance)
- Metformin



Aging, longevity , big business, science

Case study: comparing Fasting and a Fasting mimetic sirt-food shot: Microbiota, epigenetics

STOFF	WIRKSTOFF	MENGE / 25ML	Wirkstoff
Blueberry Extract	Anthocyanins/ Anthocyanidin..	40 mg	14mg 10mg
Broccoli Extract	Sulpharapane, Glucoraphin..	30 mg	
Apfel extract	Phlorentin, Quercetin..	50 mg	
Citrus extract	Naringin..	40 mg	
Nikotinamid	Nikotinamid ribosid	24 mg	
Zinkgluconat	Zink	7.5 mg	

Wasser, Stevia, Erythrit

International Journal of Molecular Sciences
MDPI
Article

Five Days Periodic Fasting Elevates Levels of Longevity Related *Christensenella* and Sirtuin Expression in Humans

Stephanie Lilja [1], Carina Stoll [1], Ulrike Krammer [1], Berit Hippe [1], Kalina Duszka [1], Tewodros Debebe [1], Ingrid Hötzinger [1], Jürgen König [1], Angelika Pointner [1] and Alexander Haslberger [1,*]

Buchinger Fasting < 120 kcal/day
n: 22 in Pernegg Monastery

Feces , blood spots, before and
After the end, first solid feces

Active (N. 131) Placebo (n: 30)
Intervention 3 months

Feces, Blood spots before, after 1,3 month

Illuminia sequencing, Line 1 methylation bisulfite qPCR, HR-MCA,
RNA, MiRNA RT QPCRi

positive correlation of the abundance of butyrate-producing *Bacteroidetes* with Mir125, siRT-1 expression, telomere length

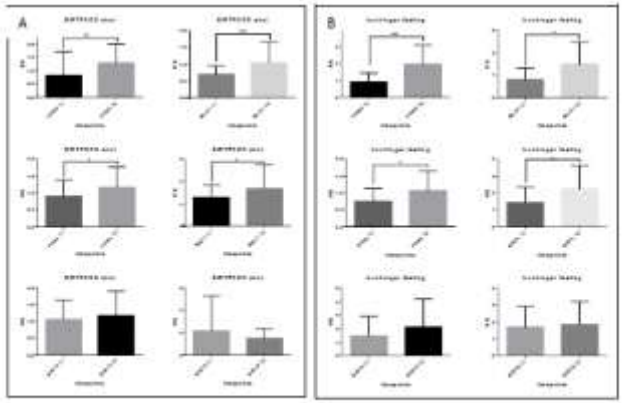


Figure 4: RQ selected mRNA gene expression (*FoxO1, MLH1, PDK4, SIRT2, SIRT3, SIRT6*) SIRTFOOD shot and buchinger fasting. The results are expressed as mean +/- SD. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

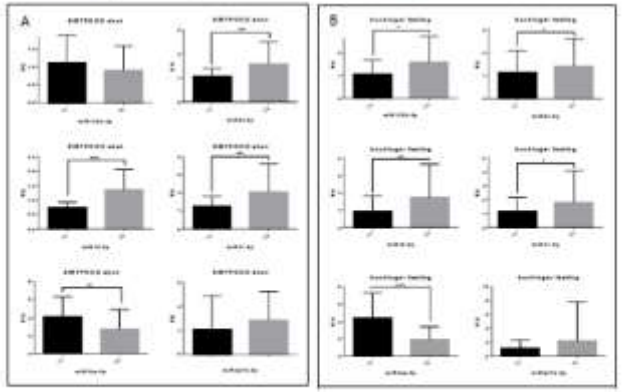


Figure 5: RQ selected miRNA gene expression (*miR125b-5p, miR99-5p, miR16-5p, miR22-3p, miR34a-3p, miRlet7b-5p*) SIRTFOOD shot and buchinger fasting. The results are expressed as mean +/- SD. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

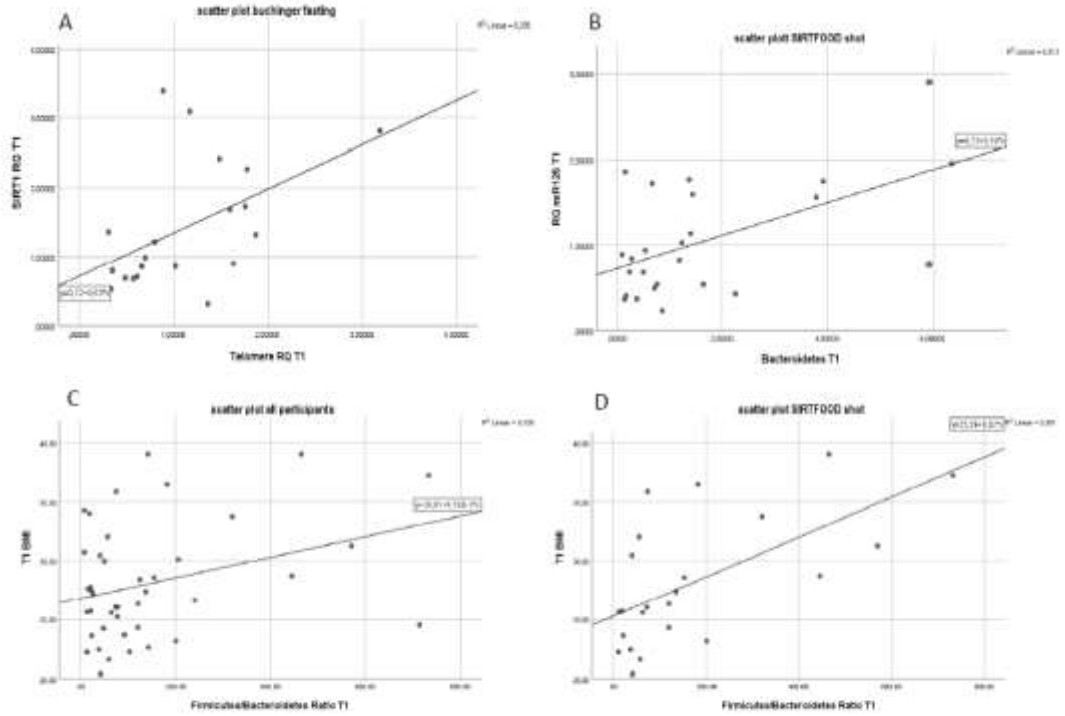


Figure 8: spss output scatter plots. (A) shows a positive correlation between telomere length and SIRT1 expression for buchinger fasting at baseline. Bacteroidetes and miR125b-5p positively correlated in the SIRTFOOD shot intervention at baseline(B). For all participants the ratio of Firmicutes/Bacteroidetes increased with higher BMI (C), which was also seen for the SIRTFOOD shot intervention Discussion (D). Statistical significance was defined as $p < 0.05$.

Buchinger fasting resulted in a rise in the distribution of Proteobacteria, increased microbiota diversity and a significant increase in Christensenella

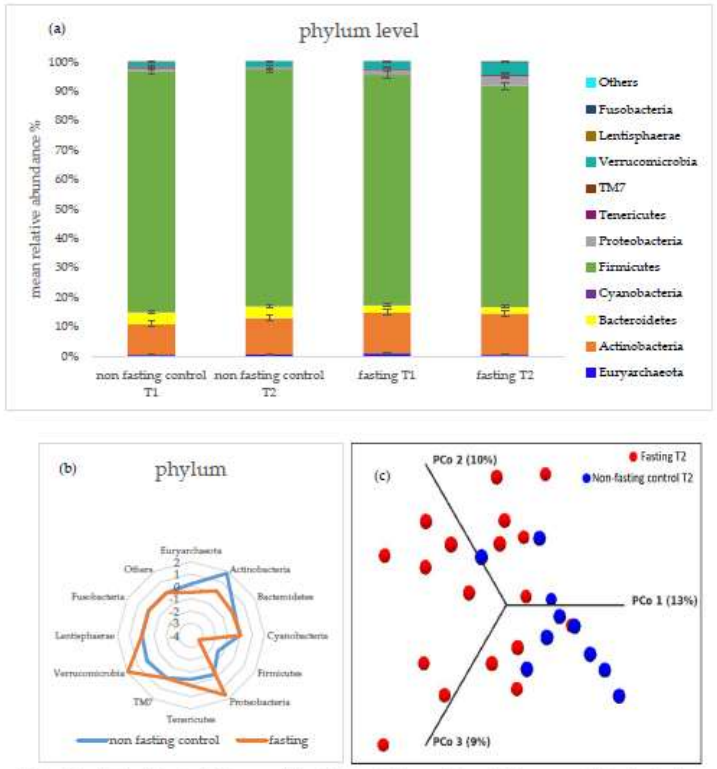


Figure 4. The dissimilarity of the microbiota composition of the non-fasting control and fasting group. (a) Bar charts of sequencing data given in mean +/− SD relative bacteria abundance in % at phylum level for non-fasting and fasting group. (b) Major differences between non-fasting and fasting groups at the phylum level. Values are given as the mean abundance of T2–T1. (c) PCoA based on Bray–Curtis dissimilarity index showing cluster for fasting and non-fasting group at T2. Permutational multivariate analysis of variance (PERMANOVA; $p = 0.00004$) was applied for the analysis.

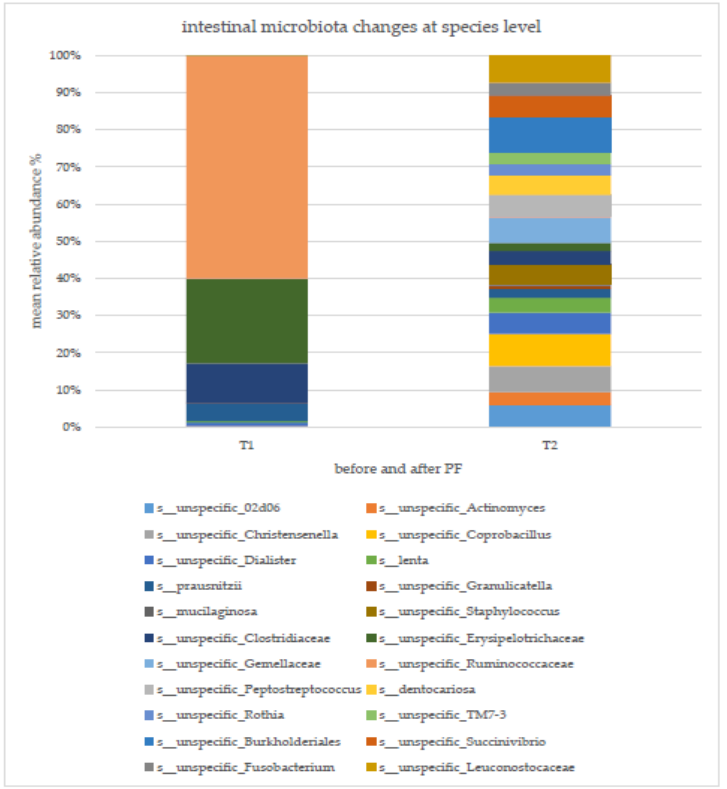


Figure 5. Microbial changes at species level before and after PF. Bar charts of all statistically significant changes of the sequencing data at species level given in mean relative bacteria abundance in % for the fasting group. Statistical significance was determined using paired *t*-test for parametric values and Wilcoxon test for nonparametric values and defined as $p < 0.05$.

3M sirt inducing drink increased *Actinobacteria.* Firmicutes*/Bacteroidetes* ratio decreased and correlated with BMI. Only Fasting increased Butyrate significantly

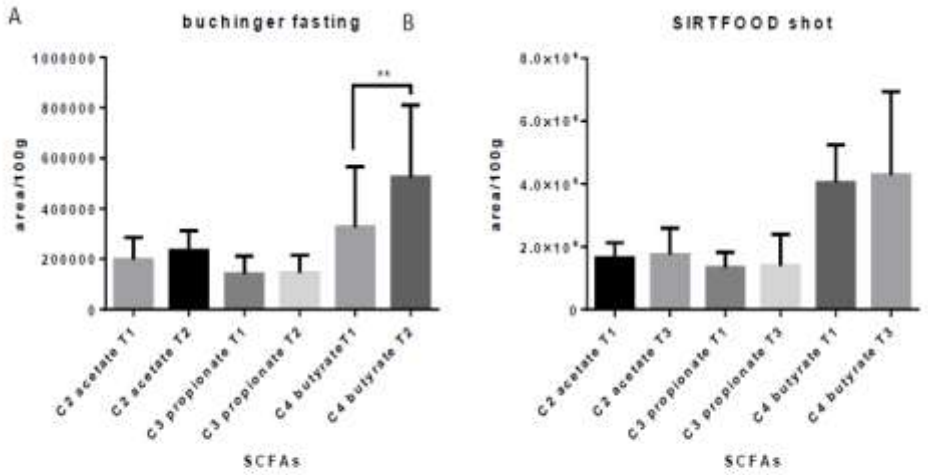


Figure 7: Amount of SCFAs produced given as area/100g stool for buchinger fasting (A) and SIRTFOOD shot (B) interventions. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

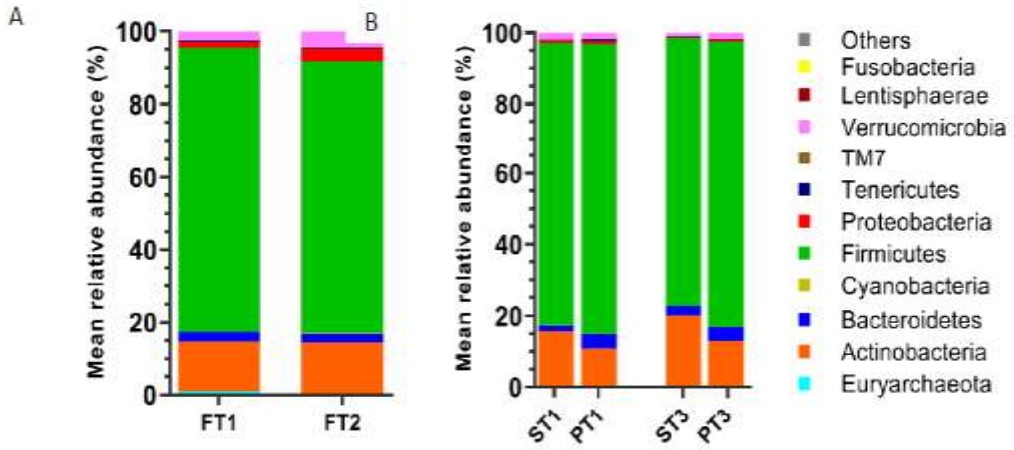


Figure 6: Abundance microbiota by phyla for fasting group (A), SIRTFOOD shot (ST1 vs ST3) (B) and placebo group (PT1 vs PT3) (B). Results are expressed in percentage of the mean of relative abundance for the different phyla. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

STUDY SENOLYTICS, SENESCENCE MARKERS IN BRDU TREATED PRE-ADIPOCYTES, ADIPOCYTES, 3T3

Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2020, Article ID 4793125, 13 pages
https://doi.org/10.1155/2020/4793125

Hindawi

Research Article

Epigallocatechin Gallate Effectively Affects Senescence and Anti-SASP via *SIRT3* in 3T3-L1 Preadipocytes in Comparison with Other Bioactive Substances

Stephanie Lilja,[1] Julia Oldenburg,[1] Angelika Pointner,[1] Laura Dewald,[1] Mariam Lerch,[1] Berit Hippe,[2] Olivier Switzeny,[2] and Alexander Haslberger[1]

EGCG Uji-XP™

Anthocyanins-Bluezones®

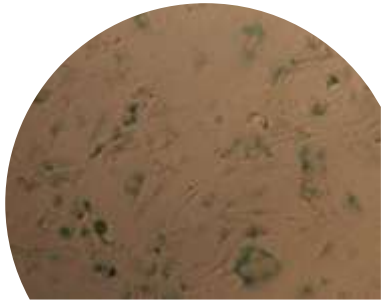
Ayurvedic Spermidine Bluezones®

BLUEZONES™ RESVERATROL

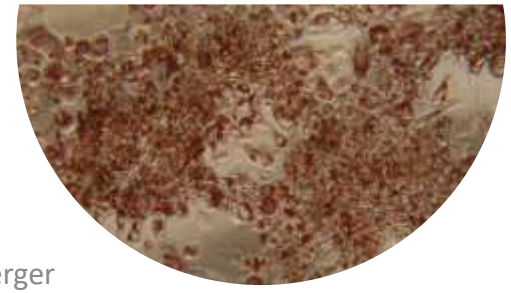
Phloretin, BHB, Butyrate (Merck)

Stem Cells. Author manuscript; available in PMC 2015 Aug 19.
Published in final edited form as:
Stem Cells. 2008 Dec; 26(12): 3218–3227.
Published online 2008 Sep 18. doi: 10.1634/stemcells.2008-0299

Bromodeoxyuridine Induces Senescence



B-Gal, senescence



Adipocytes, fat droplets

CR, fasting mimetics, senolytics

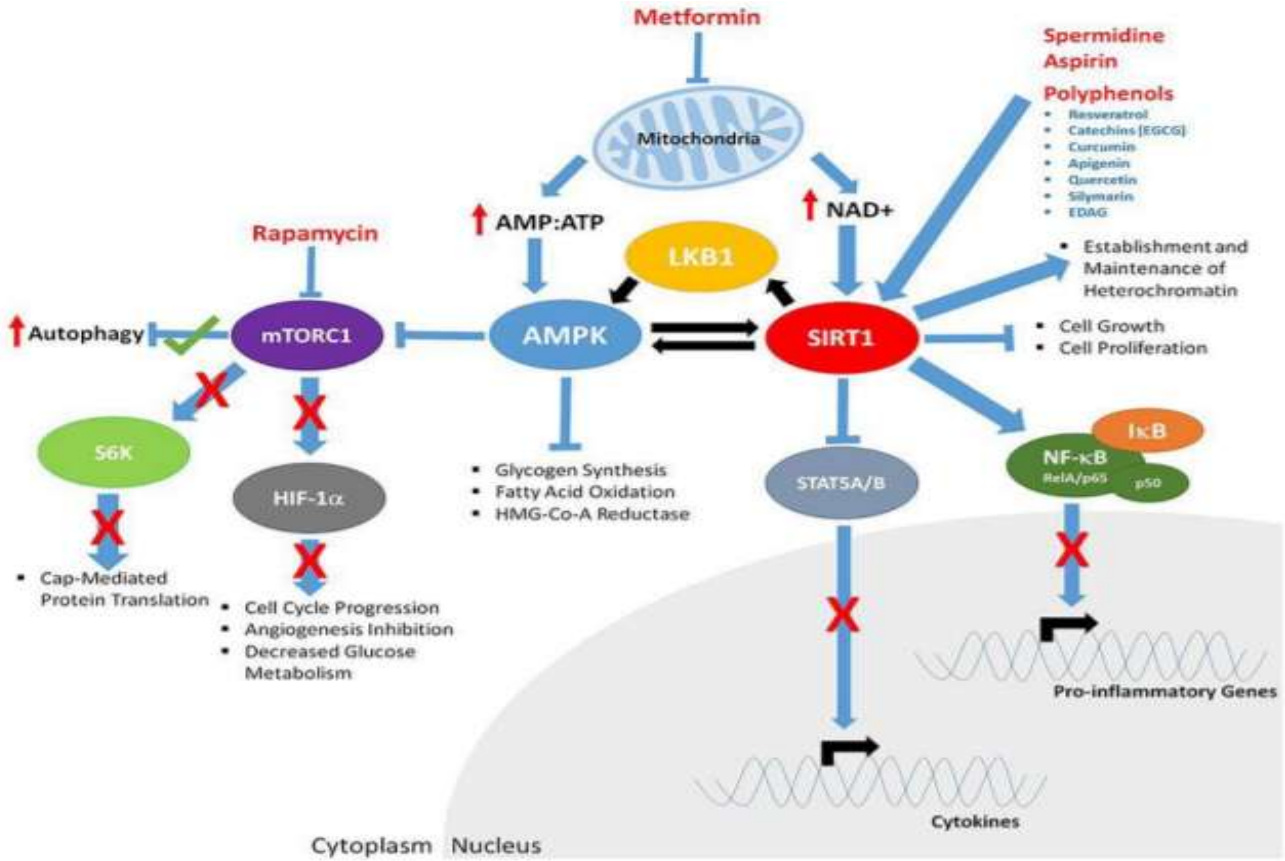
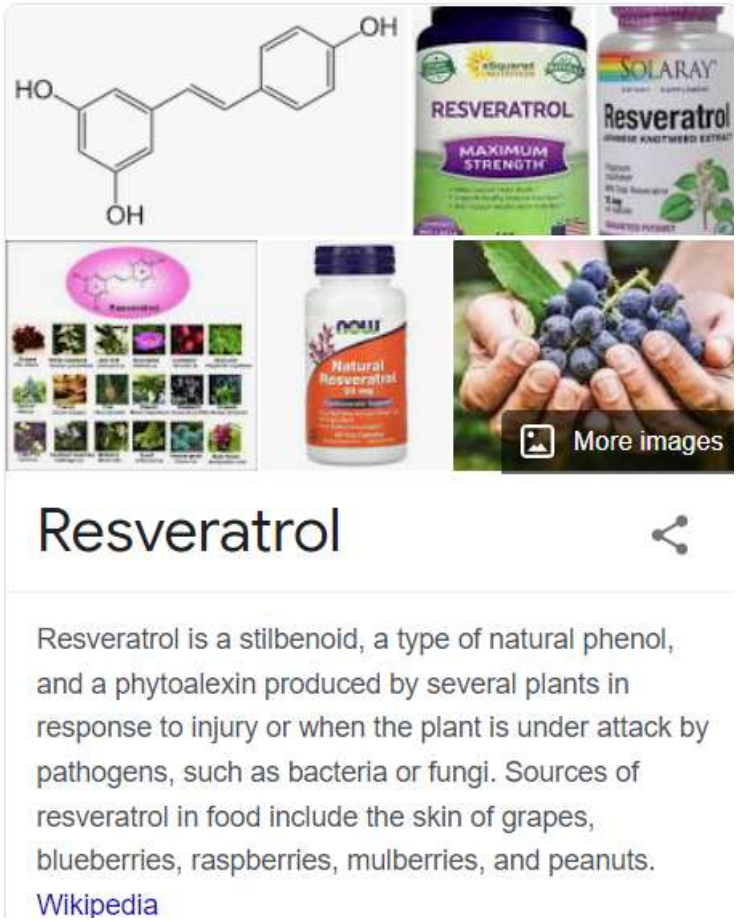
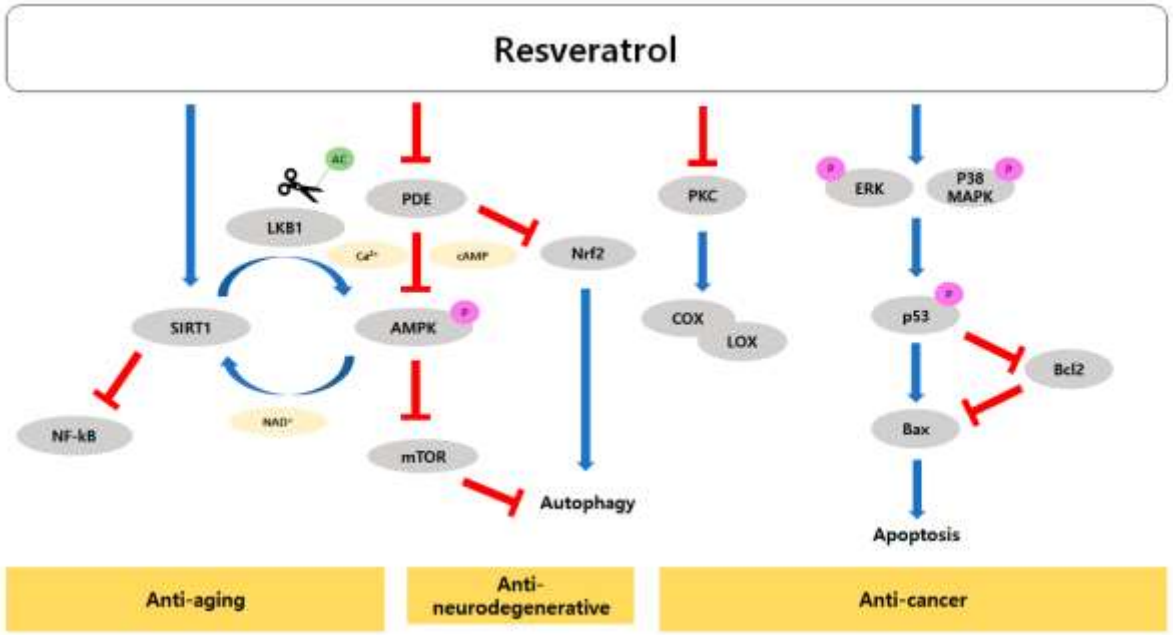


Figure 20. The downstream effects of CR mimetics and nutraceuticals on key aging mediators AMPK and SIRT1 [177].

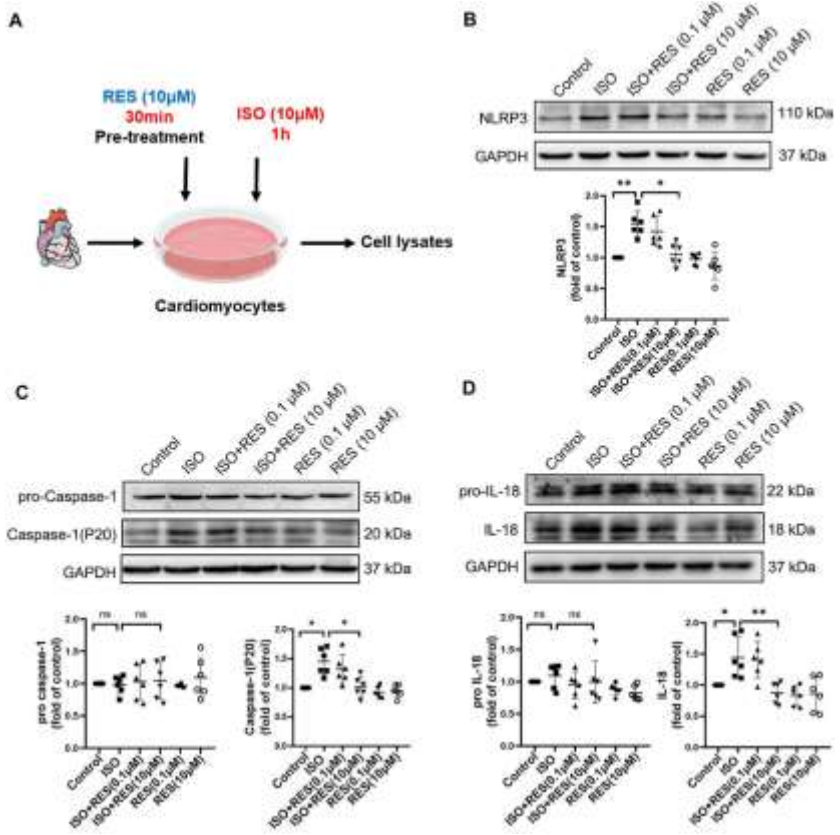
Examples, Resveratrol

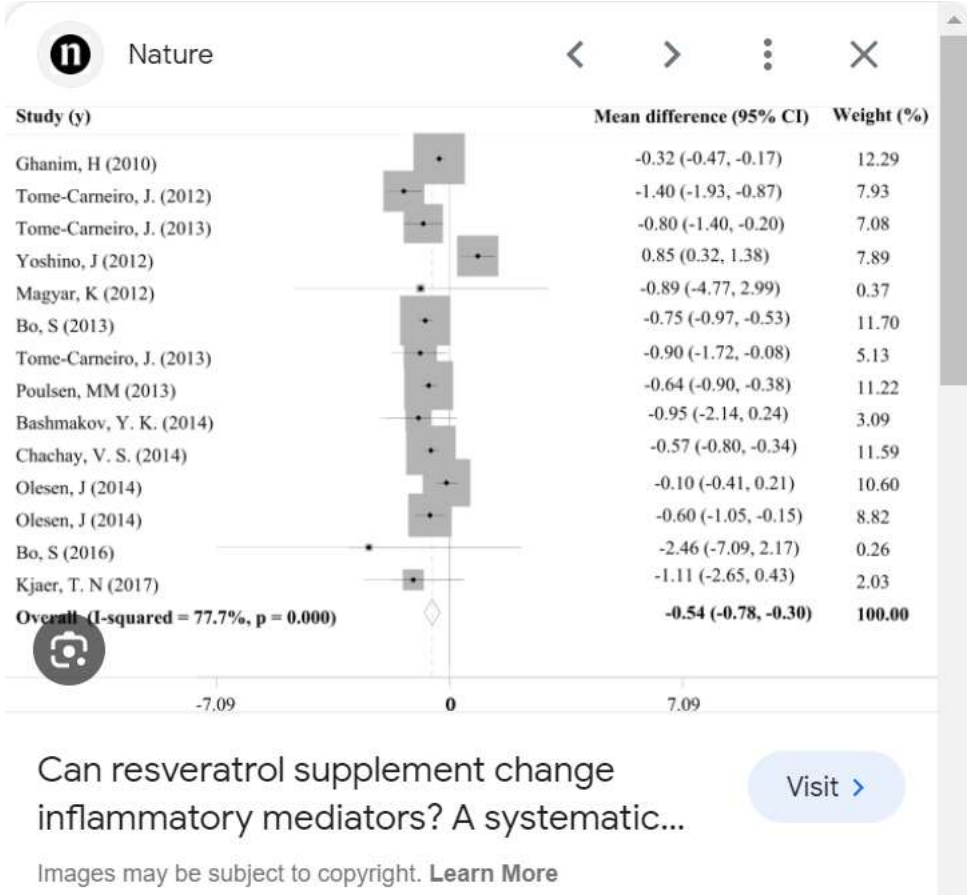


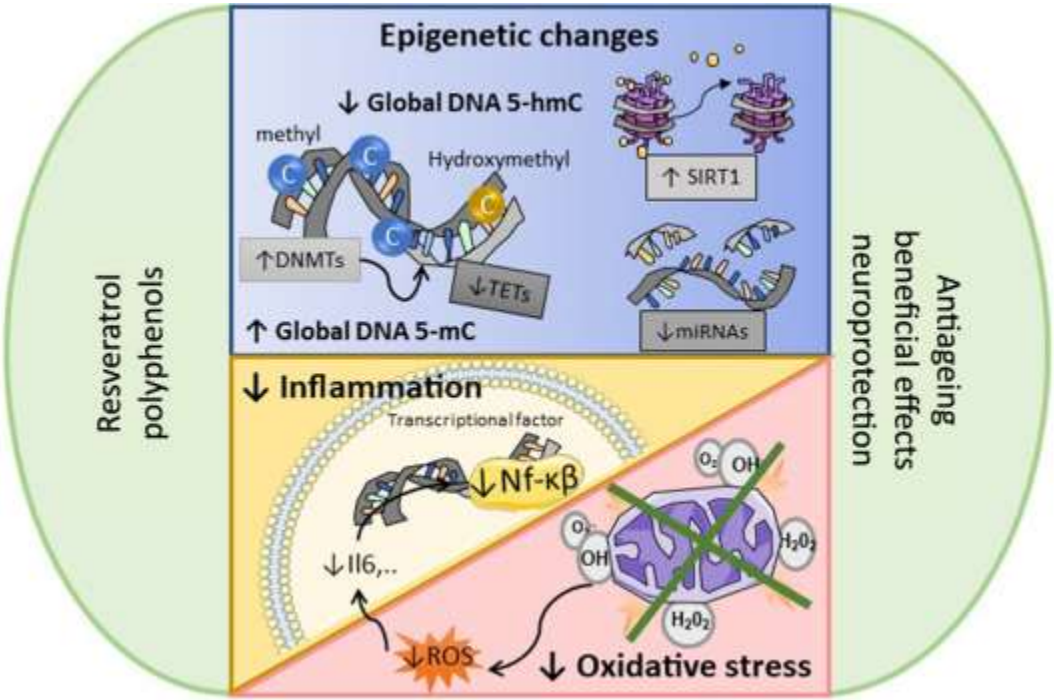


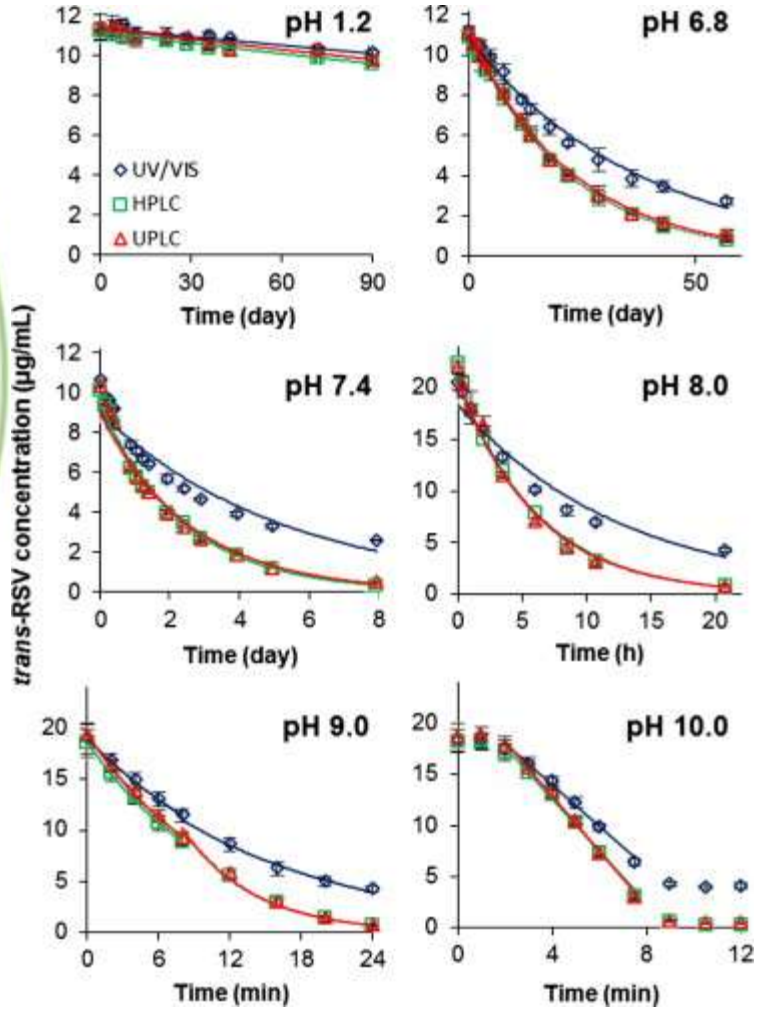
Previous studies have demonstrated that resveratrol is well-absorbed following oral administration, with ~75% of the dose absorbed. Following absorption, resveratrol undergoes rapid and extensive metabolism leading to low bioavailability

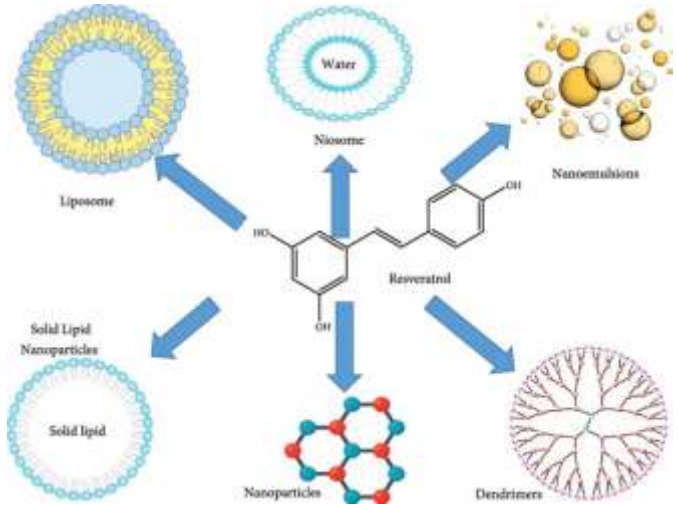
Resveratrol Vitro : Vivo





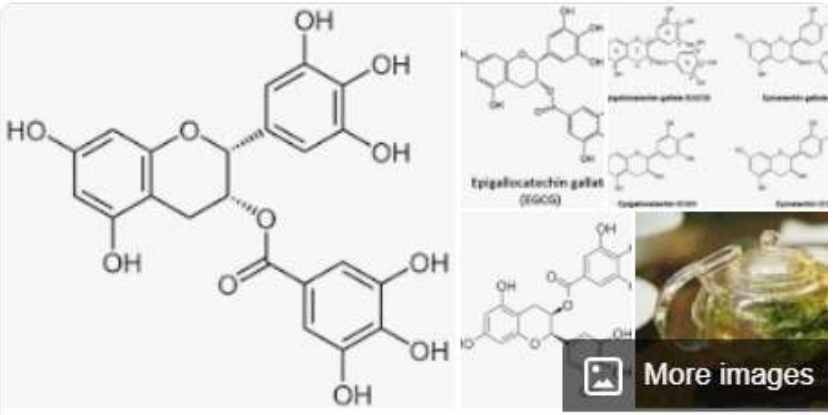

Resveratrol polyphenols
Epigenetic changes
↓ Global DNA 5-hmC
methyl
Hydroxymethyl
↑ SIRT1
↑DNMTs
↓TETs
↑ Global DNA 5-mC
↓miRNAs
↓ Inflammation
Transcriptional factor
↓Nf-κβ
↓Il6,..
↓ROS
↓ Oxidative stress
Antiageing beneficial effects neuroprotection


pH 1.2
pH 6.8
pH 7.4
pH 8.0
pH 9.0
pH 10.0
UV/VIS
HPLC
UPLC
trans-RSV concentration (μg/mL)
Time (day)
Time (h)
Time (min)


Water
Niosome
Liposome
Nanoemulsions
Resveratrol
Solid Lipid Nanoparticles
Solid lipid
Nanoparticles
Dendrimers

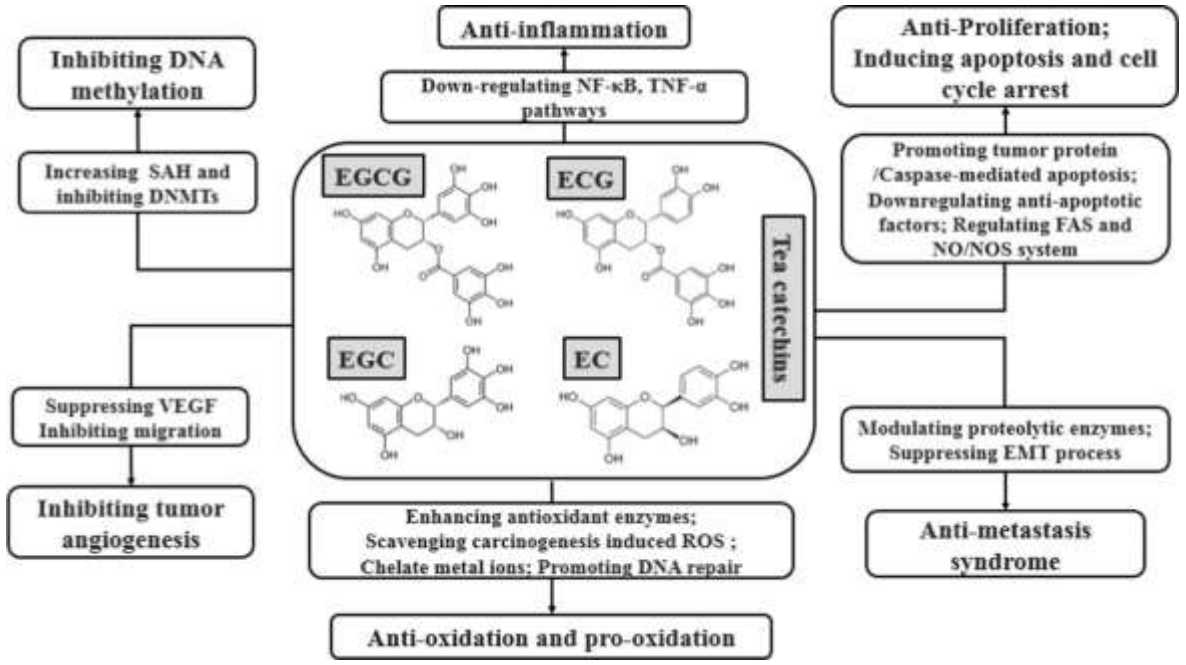
Novel food ?!

Green tea extract, EGCG, Catechines

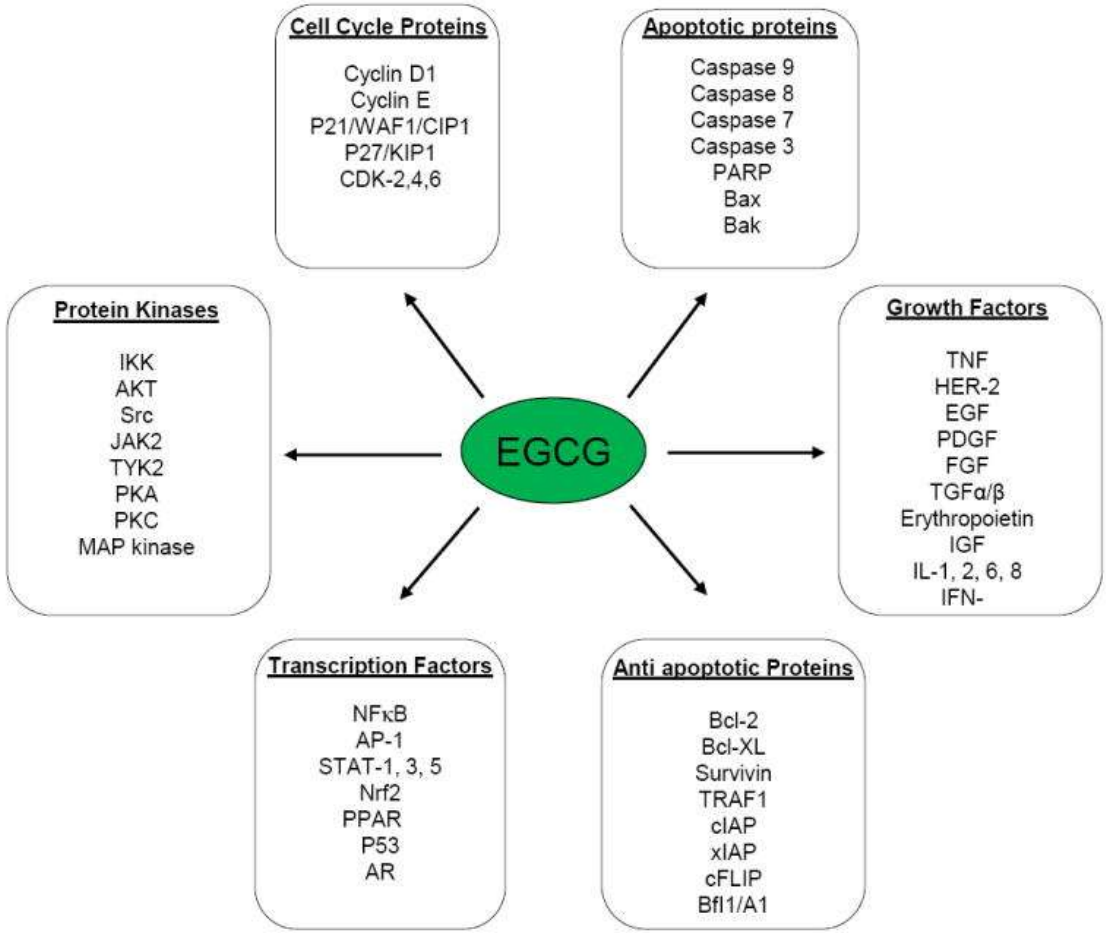


Epigallocatechin gallate

Epigallocatechin gallate, also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid, and is a type of catechin. EGCG – the most abundant catechin in tea – is a polyphenol under basic research for its potential to affect human health and disease. Wikipedia



EGCG


Cell Cycle Proteins
Cyclin D1
Cyclin E
P21/WAF1/CIP1
P27/KIP1
CDK-2,4,6
Apoptotic proteins
Caspase 9
Caspase 8
Caspase 7
Caspase 3
PARP
Bax
Bak
Protein Kinases
IKK
AKT
Src
JAK2
TYK2
PKA
PKC
MAP kinase
EGCG
Growth Factors
TNF
HER-2
EGF
PDGF
FGF
TGFα/β
Erythropoietin
IGF
IL-1, 2, 6, 8
IFN-
Transcription Factors
NFκB
AP-1
STAT-1, 3, 5
Nrf2
PPAR
P53
AR
Anti apoptotic Proteins
Bcl-2
Bcl-XL
Survivin
TRAF1
cIAP
xIAP
cFLIP
Bfl1/A1

EGCG II

FFHD
Functional Foods in Health and Disease

The green tea polyphenol EGCG is differentially associated with telomeric regulation in normal human fibroblasts versus cancer cells

Angelika Pointner[1], Christine Mölzer[1,2], Ulrich Magnet[1], Katja Zappe[1,3], Berit Hippe[1], Anela Tosevska[1,4], Elena Tomeva[1], Elisabeth Dum[1], Stephanie Lilja[1], Ulrike Krammer[1], Alexander Haslberger[1*]

Research Article

EGCG Prevents High Fat Diet-Induced Changes in Gut Microbiota, Decreases of DNA Strand Breaks, and Changes in Expression and DNA Methylation of *Dnmt1* and *MLH1* in C57BL/6J Male Mice

Marlene Remely,[1] Franziska Ferk,[2] Sonja Sterneder,[1] Tahereh Setayesh,[2] Sylvia Roth,[1] Tatjana Kepcija,[1] Rahil Noorizadeh,[2] Irene Rebhan,[1] Martina Greunz,[1] Johanna Beckmann,[1] Karl-Heinz Wagner,[1] Siegfried Knasmüller,[2] and Alexander G. Haslberger[1]

Research Article

Epigallocatechin Gallate Effectively Affects Senescence and Anti-SASP via *SIRT3* in 3T3-L1 Preadipocytes in Comparison with Other Bioactive Substances

Stephanie Lilja,[1] Julia Oldenburg,[1] Angelika Pointner,[1] Laura Dewald,[1] Mariam Lerch,[1] Berit Hippe,[2] Olivier Switzeny,[2] and Alexander Haslberger[1]

Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice

Joshua D Lambert [1], Jungil Hong, Dou Hwan Kim, Vladimir M Mishin, Chung S Yang

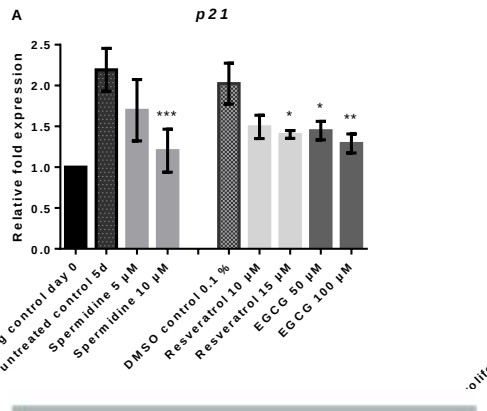
Affiliations + expand

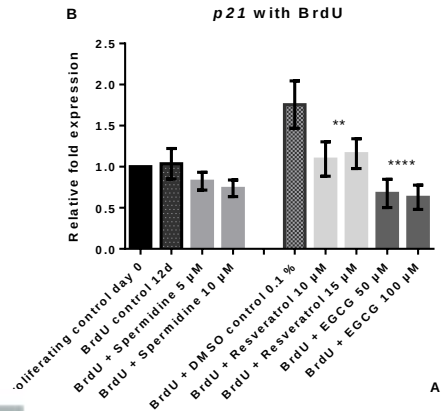
PMID: 15284381 DOI: 10.1093/jn/134.8.1948

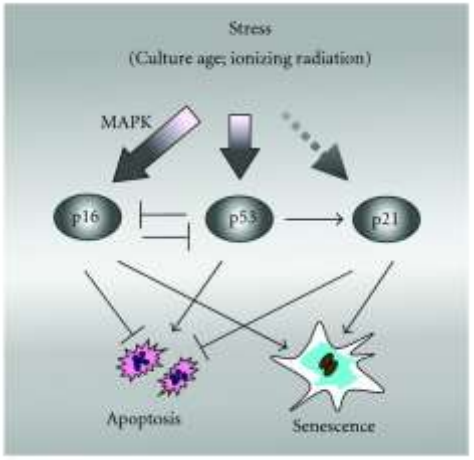
Abstract

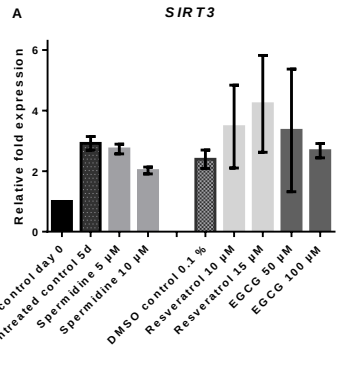
(-)-Epigallocatechin-3-gallate (EGCG), from green tea (Camellia sinensis), has demonstrated chemopreventive activity in animal models of carcinogenesis. Previously, we reported the bioavailability of EGCG in rats (1.6%) and mice (26.5%). Here, we report that cotreatment with a second dietary component, piperine (from black pepper), enhanced the bioavailability of EGCG in mice. Intragastric coadministration of 163.8 micromol/kg EGCG and 70.2 micromol/kg piperine to male CF-1 mice increased the plasma C(max) and area under the curve (AUC) by 1.3-fold compared to mice treated with EGCG only. Piperine appeared to increase EGCG bioavailability by inhibiting glucuronidation and gastrointestinal transit. Piperine (100 micromol/L) inhibited EGCG glucuronidation in mouse small intestine (by 40%) but not in hepatic microsomes. Piperine (20

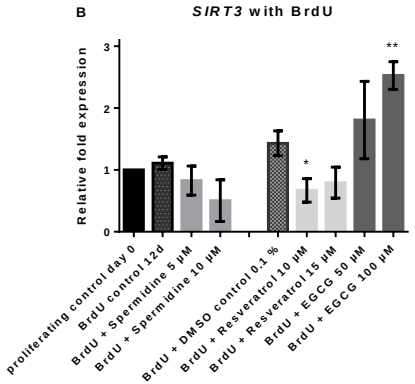
Egcg Effectively reduce Senescence (p21) and SASP
EGCG, spermidine, resveratrol, anthocyans stimulate SIRT3



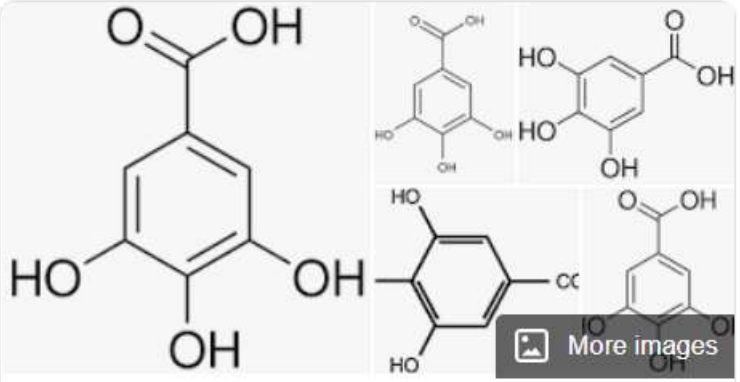








Gallic acid



Gallic acid

Gallic acid is a trihydroxybenzoic acid with the formula $C_6H_2(OH)_3CO_2H$. It is classified as a phenolic acid. It is found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants. It is a white solid, although samples are typically brown owing to partial oxidation.
Wikipedia

Gallic acid, a common dietary phenolic protects against high fat diet induced DNA damage

Tahereh Setayesh[1] · Armen Nersesyan[1] · Miroslav Mišík[1] · Rahil Noorizadeh[1,3] · Elisabeth Haslinger[1] · Tahereh Javaheri[2,3] · Elisabeth Lang[1] · Michael Grusch[1] · Wolfgang Huber[1] · Alexander Haslberger[4] · Siegfried Knasmüller[1]

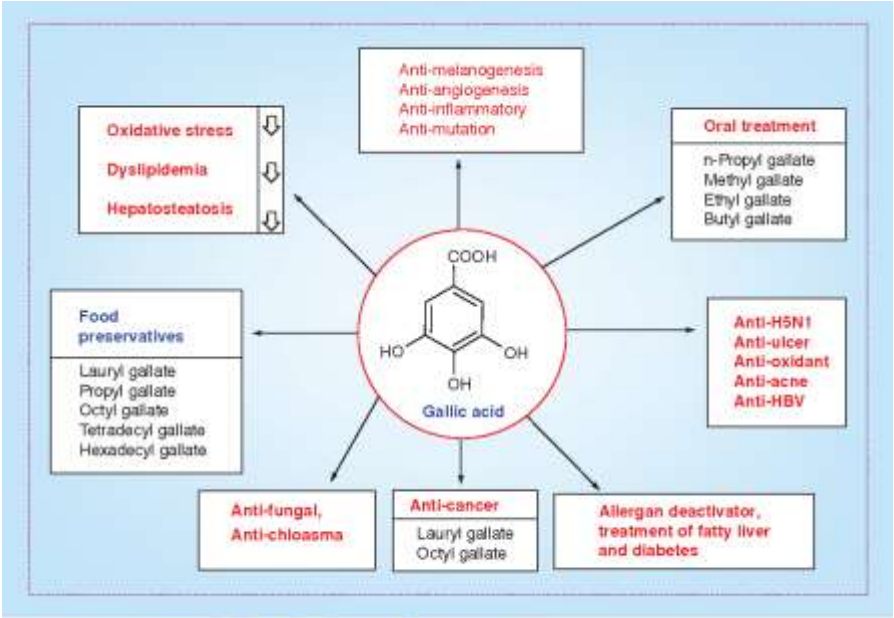


Figure 2. Important uses of gallic acid and its ester derivatives.

Astaxanthin

Astaxanthin

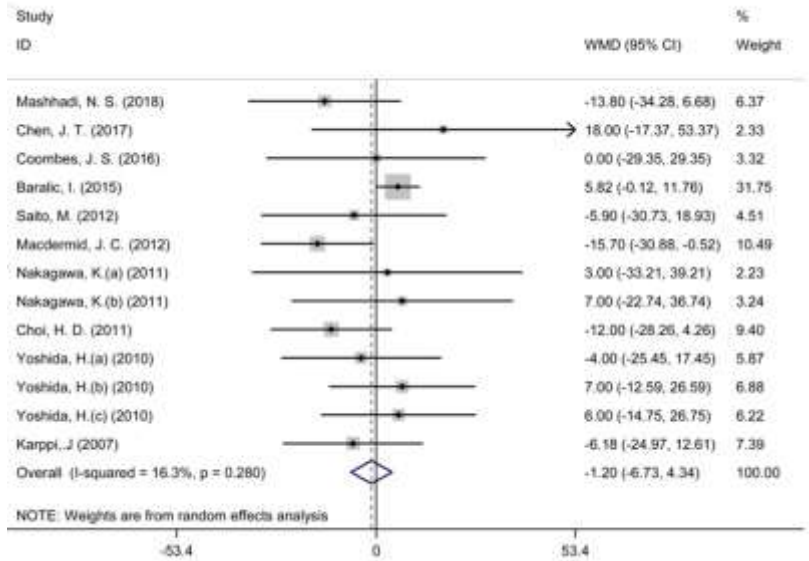
Chemical compound

Astaxanthin is a keto-carotenoid with various uses including dietary supplement and food dye. It belongs to a larger class of chemical compounds known as terpenes built from five carbon precursors, isopentenyl diphosphate, and dimethylallyl diphosphate. Wikipedia

Astaxanthin ist ein natürlicher, orangeroter Farbstoff. Er zählt zu den Carotinoiden, genauer gesagt zu den sauerstoffhaltigen Xanthophyllen. Das sind farbige Inhaltsstoffe bestimmter Pflanzen. Es wurde früher auch als Hämatochrom bezeichnet (von altgriechisch „haima“ für „Blut“ und „chroma“ für „Farbe“). Die Substanz wird hauptsächlich von Mikroalgen wie der Blutregenalge (Haematococcus pluvialis), aber auch der roten Hefe Phaffia rhodozyma und dem Bakterium Paracoccus carotinifaciens gebildet.1

Astaxanthin dient der Alge als natürlicher UV-Schutz und als Molekül zur Nährstoffbindung: Um unter schwierigen Umweltbedingungen wie starker Sonneneinstrahlung, Wasser- oder Sauerstoffmangel zu überleben, stellt sie ihre Stoffwechselvorgänge ein und bildet zum Schutz eine blutrote Zyste, deren Pigmente aus Astaxanthin bestehen.2

Das Carotinoid ist jedoch nicht nur im Plankton enthalten, sondern gelangt über die Nahrungskette in das Tierreich. Wassertiere wie Lachs, Garnelen, Forellen, Krill oder Krebse, aber auch Flamingos fressen die Mikroalge. Sie erhalten durch Astaxanthin ihre rötliche Färbung und schützen sich damit ebenfalls vor den schädlichen Auswirkungen von UV-Licht und aggressiven Sauerstoffradikalen.3 Der Nährstoff ist auch ein wichtiger Zusatz in Futtermitteln und hilft bei der gesunden Aufzucht von Jungfischen.4



FBS	HbA1c	TC	LDL-C	TG	BMI	BW	DBP	SBP	HDL-C	CRP
									↑	↓

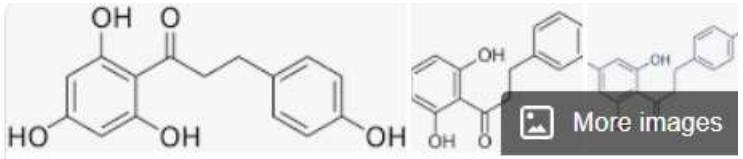
Quercetin

Quercetin

Quercetin is a plant flavonol from the flavonoid group of polyphenols. It is found in many fruits, vegetables, leaves, seeds, and grains; capers, red onions and kale are common foods containing appreciable amounts of quercetin. Wikipedia

Quercetin Benefits	Additional Information
Anti-inflammatory and Immune Boosting Research has shown that quercetin displays anti-inflammatory and immune strengthening capabilities. One study even shows how quercetin was able to mitigate the inflammatory responses stimulated by the popular food additive carrageenan. Quercetin was also shown to be able to decrease the clinical indicators of arthritis.	**Recommended daily intake** • 200-250 mg/day or even lower. • Research shows that even small amounts are effective for everyday consumption.
Possible Cancer fighting properties Studies have shown that quercetin was able to restrain the growth of cancer and as such prevent the proliferation of cancer cells especially as it relates to certain types of cancers – colorectal, ovarian and breast cancer cells.	**Some foods that are high in quercetin** • Onions • Shallots • Asparagus • Green peppers • Tomatoes • Apples • Cranberries
Cardiovascular Health Research shows that quercetin was able to reduce some of the major risks factors of heart disease such as high blood pressure, oxidative stress and inflammation.	
Anti-viral properties Studies have shown that quercetin was effective in the prevention of viral or respiratory conditions as well as well as fight against viruses such as herpes and parainfluenza type 3.	**Possible side effects** • Headaches • Stomach discomfort • Kidney damage (high doses).
Asthma Research shows that quercetin is able to reduce inflammatory cells of the immune system as well as decrease the histamine levels which then helps to smooth the muscles of the airways and helps with breathing.	
Almondsandolivez.com	

Phloretin



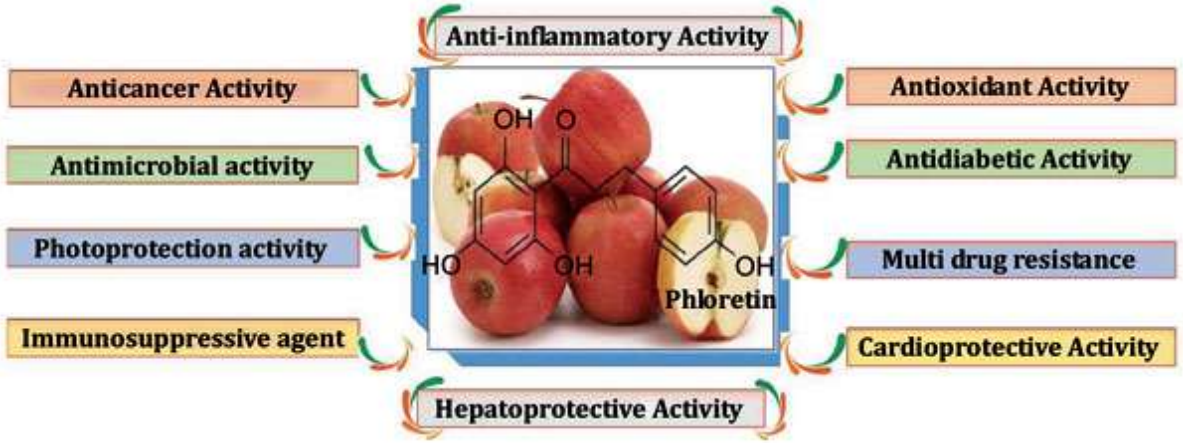
Phloretin

Phloretin is a dihydrochalcone, a type of natural phenol. It can be found in apple tree leaves and the Manchurian apricot. Wikipedia

Tabelle 1. Potenzielle chemopräventive Aktivitäten der Apfelsaftextrakte A und B[a]

	Extrakt A	Extrakt B
Mechanismen in der Initiationsphase		
DPPH-Radikalfängereigenschaften (IC_{50})[b]	8.7 µg/ml	10.5 µg/ml
Peroxyl-Radikalfängereigenschaften (ORACROO)(Einheiten)[d]	2.4	1.9
Superoxid Anion Radikalfängereigenschaften (IC_{50})	17.1 µg/ml	25.8 µg/ml
Hemmung der Cyp1A Aktivität (IC_{50})[b]	11.5 µg/ml	4.3 µg/ml
Induktion der NAD(P)H:Chinon-Reduktase-Aktivität in Hepa1c1c7-Maus-Hepatomzellen (CD)[c]	200 µg/ml	39.2 µg/ml
Hemmung der Hepa1c1c7-Zellproliferation (IC_{50})	>200 µg/ml	>200 µg/ml
Anti-Tumorpromovierende Mechanismen		
Hemmung der Aromatase Aktivität (IC_{50})	5.9 µg/ml	5.0 µg/ml
Hemmung der Cox-1-Aktivität (% Hemmung bei 400 µg/ml)	62	74
Anti-proliferative Mechanismen		
Hemmung der Proliferation von humanen HCT116-Darmkrebszellen (IC_{50})	44.3 µg/ml	35.3 µg/ml

[a] Beschreibung der Testsysteme in Gerhauser et al. 2003



Zusammenfassend lässt sich sagen, dass sowohl durch naturtrüben Apfelsaft als auch durch Apfelsaftextrakt im ApcMin/+ Maus Modell eine Verminderung der Anzahl an Adenomen im Dünndarm festgestellt werden konnte

: This study aimed to assess the inter-individual variation in phloretin absorption and metabolism
and to seek possible phloretin metabotypes following apple snack consumption. Methods: The excreted
phloretin metabolites in 24 h urine samples were determined by UPLC-MS/MS in 62 volunteers after
acute and sustained (6 weeks) interventions in a randomized and parallel study with a daily supplementation of 80 g of a low-phloretin (39.5 µmol) or a high-phloretin (103 µmol) freeze-dried apple snacks

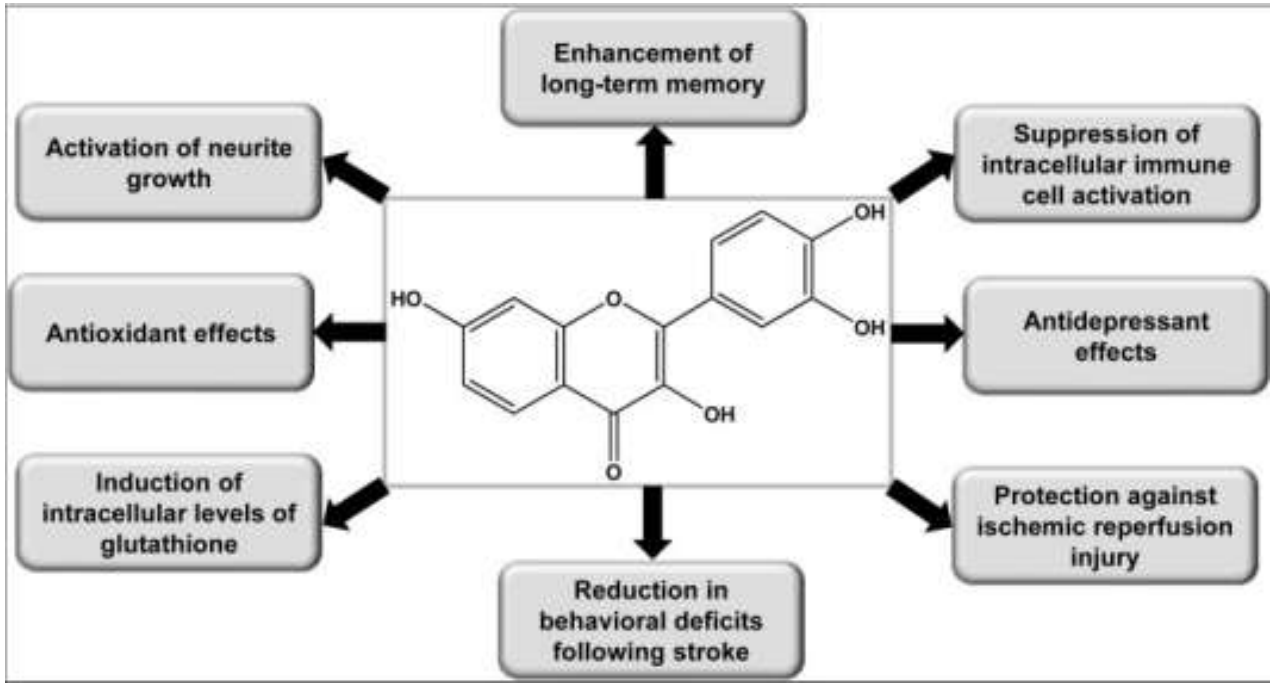
extensive interindividual variability exists in the excretion of phloretin phase-II conjugates following consumption of
apple snacks, which could be related to oral microbiota phloridzin-hydrolysing activity, lactase non-persistence trait or the metabotype to which the subject belongs. There were inconsistent effects on postprandial serum glucose concentrations but there was a tendency for decreases to be associated with
higher excretion of phloretin phase-II conjugates.

Fisetin

Fisetin

Chemical compound

Fisetin is a plant flavonol from the flavonoid group of polyphenols. It can be found in many plants, where it serves as a yellow/ochre colouring agent. It is also found in many fruits and vegetables, such as strawberries, apples, persimmons, onions and cucumbers. Wikipedia

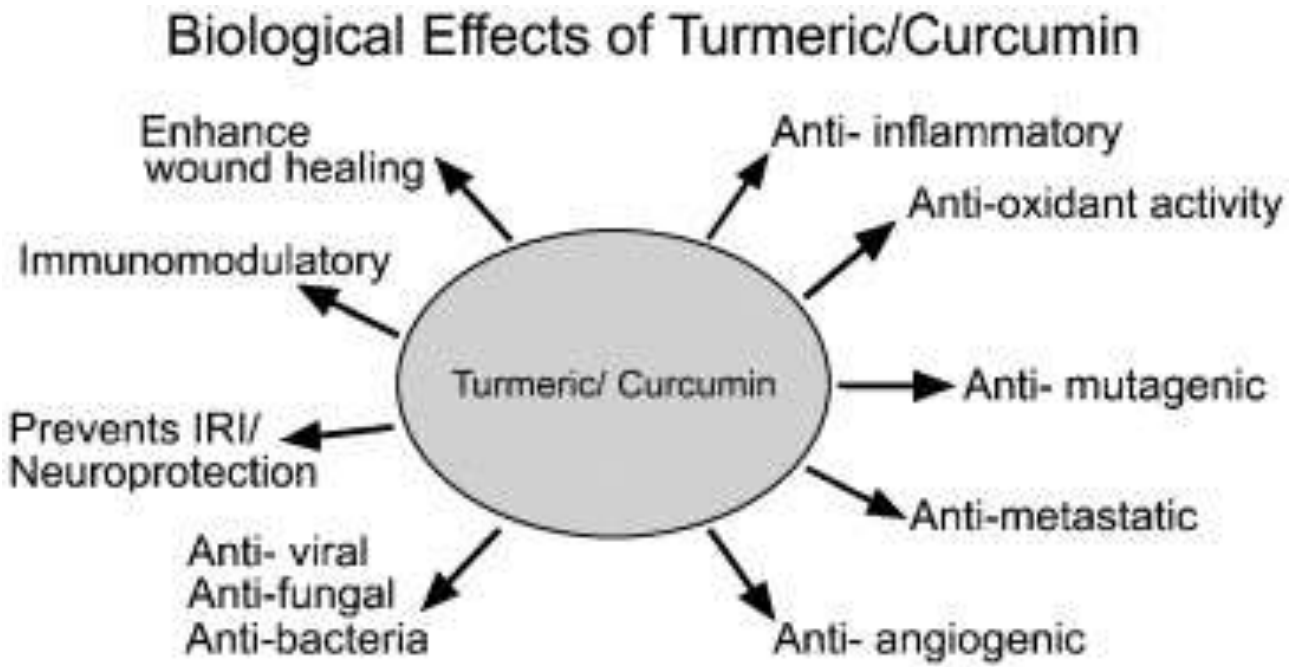


Curcumin

Curcumin

Chemical compound

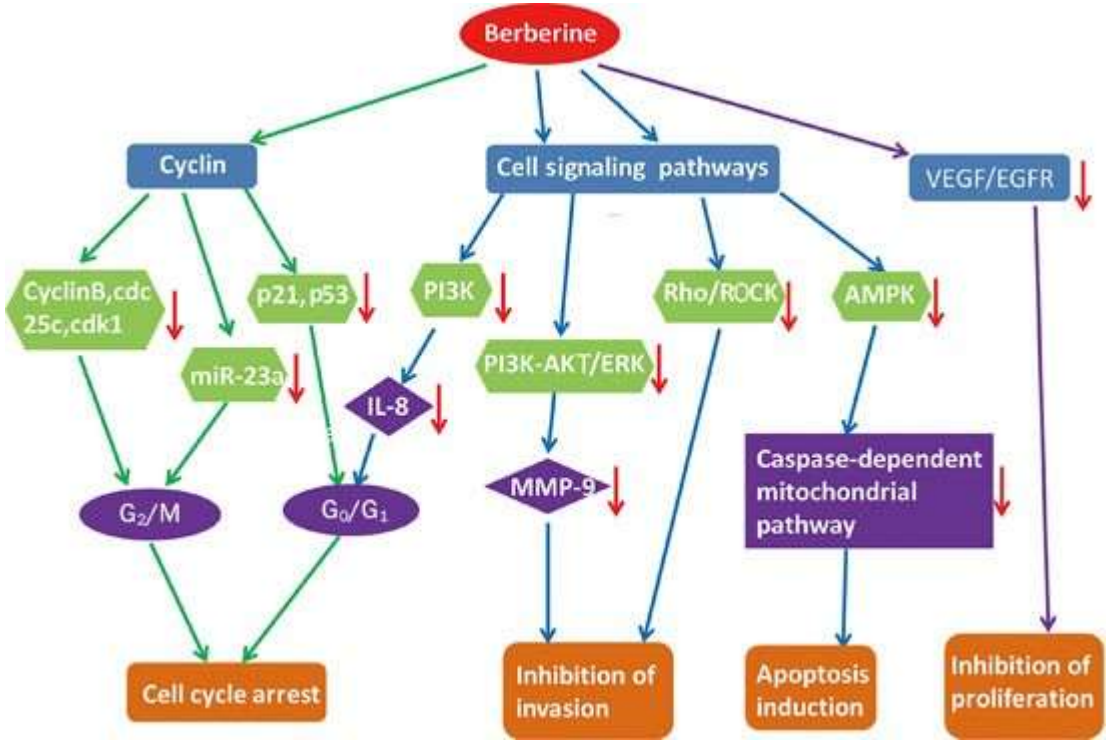
Curcumin is a bright yellow chemical produced by plants of the Curcuma longa species. It is the principal curcuminoid of turmeric, a member of the ginger family, Zingiberaceae. It is sold as an herbal supplement, cosmetics ingredient, food flavoring, and food coloring. Wikipedia



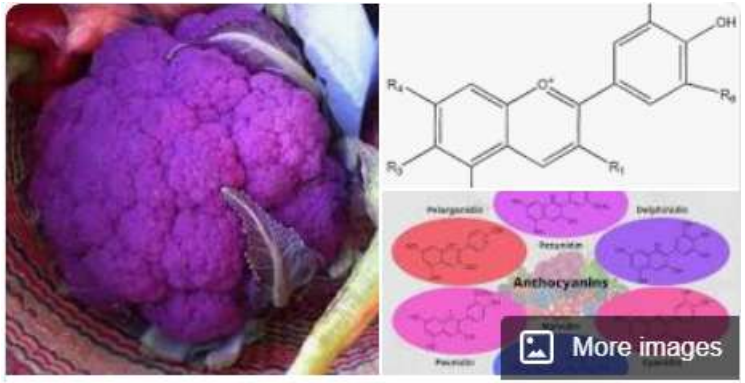
Berberin, Berberitze

Berberine (Berberin)

Berberine is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in such plants as Berberis, such as Berberis vulgaris, Berberis aristata, Mahonia aquifolium, ...
Wikipedia



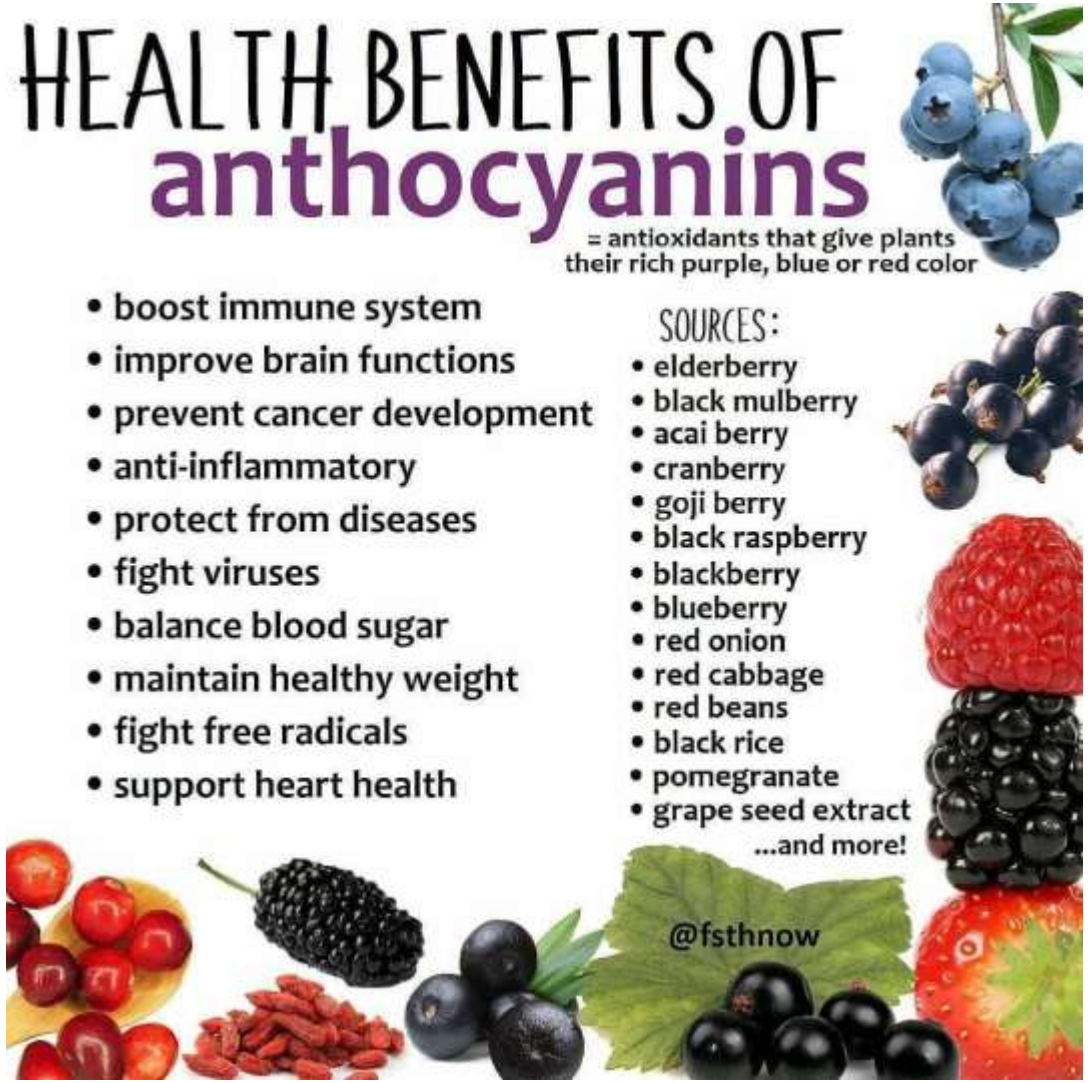
Anthocyans



Anthocyanin

Chemical compound

Anthocyanins are water-soluble vacuolar pigments that, depending on their pH, may appear red, purple, blue, or black. In 1835, the German pharmacist Ludwig Clamor Marquart gave the name Anthokyan to a chemical compound that gives flowers a blue color for the first time in his treatise “Die Farben der Blüthen”. Wikipedia

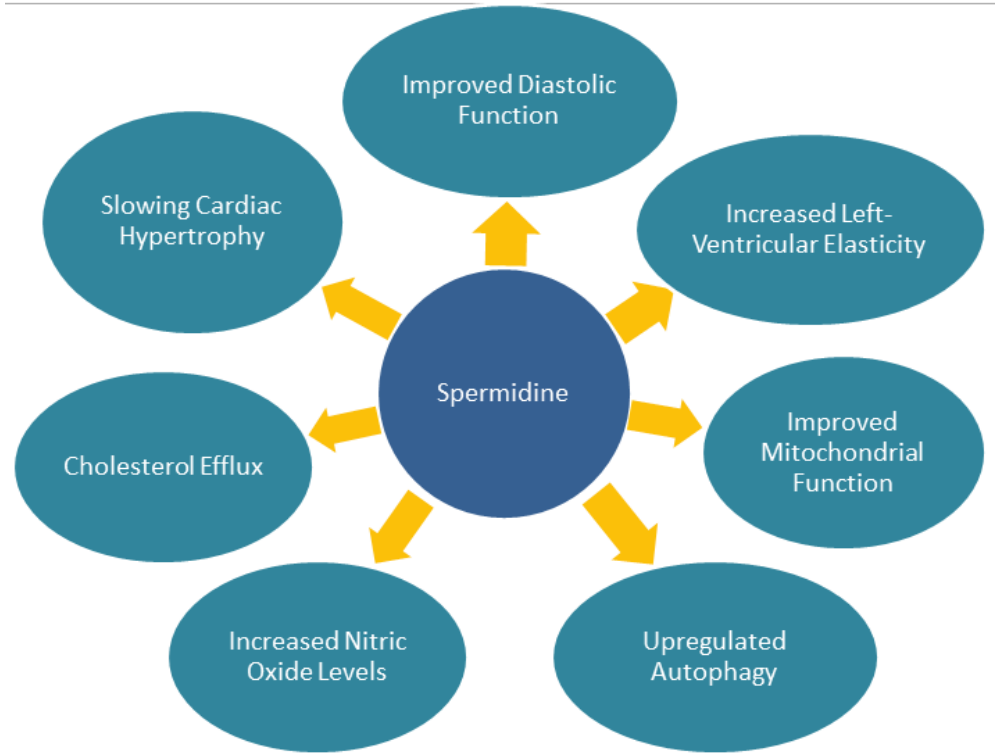


Spermidin

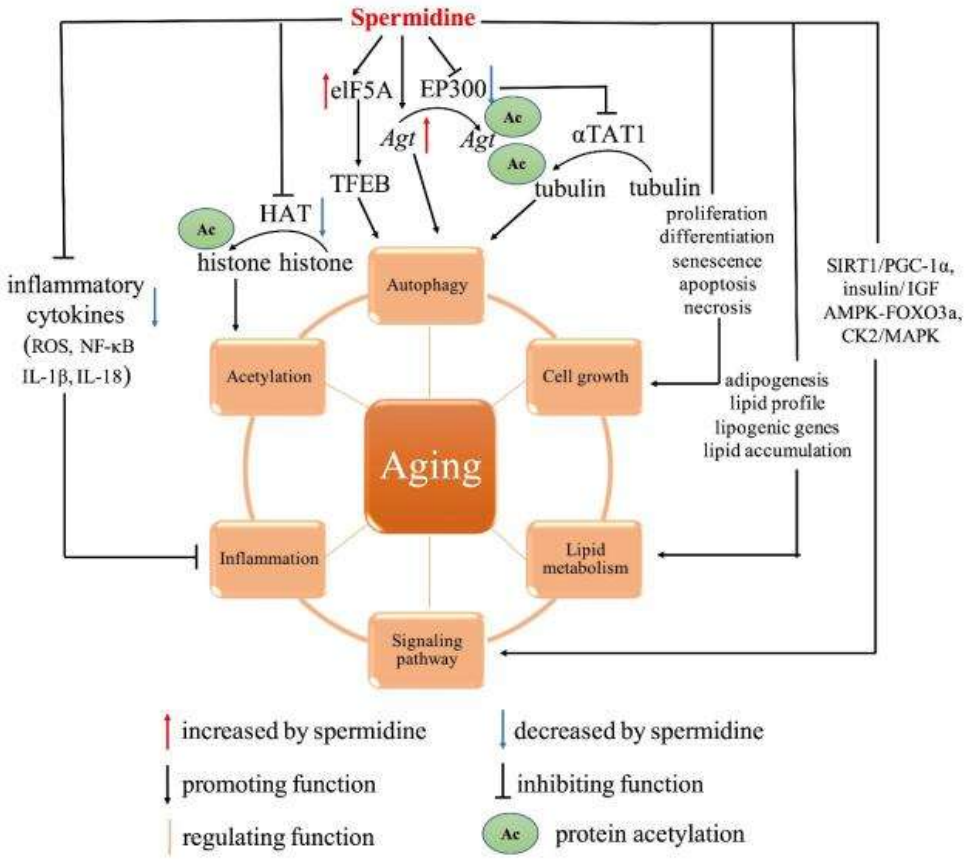
Spermidine (Spermidin)

Chemical compound

Spermidine is a polyamine compound found in ribosomes and living tissues and having various metabolic functions within organisms. It was originally isolated from semen. Wikipedia



Spermidin mechanisms



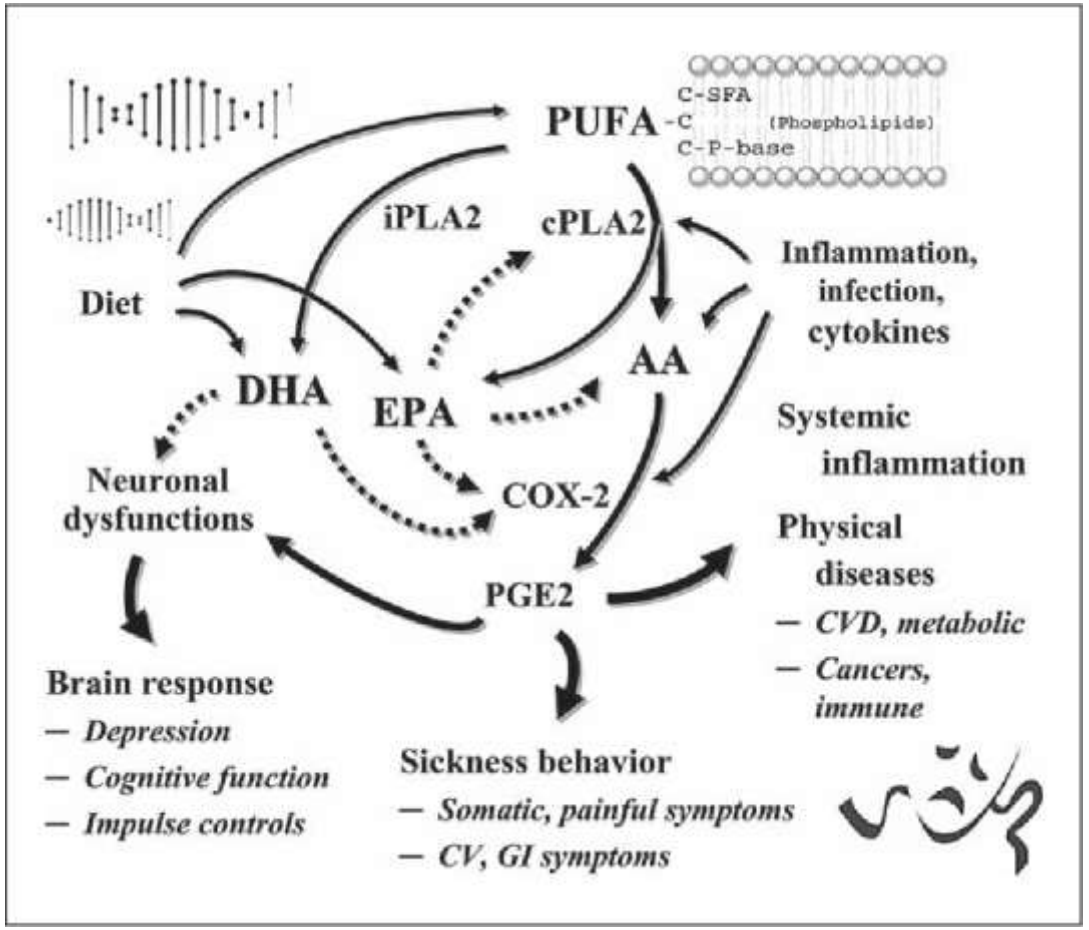
Molecular and cellular mechanisms of spermidine in age-related diseases. Spermidine is an inducer of autophagy, which is the main mechanism of anti-aging. First, spermidine **triggers autophagy by modulating the expressions of *Atg* genes**. Second, it regulates **transcription factor eIF 5A to promote the synthesis of transcription factor TFEB.** Third, spermidine **inhibits EP300, which directly promotes the acetylation of Atg genes** and **indirectly stimulates deacetylation of tubulin due to inhibition of aTAT1**. Besides, spermidine exerts potent anti-inflammatory roles by **suppressing of multiple inflammatory cytokines, such as ROS, NF-κB, IL-1β and IL-18**. Moreover, it is involved in regulation **of cell proliferation, differentiation, senescence, apoptosis and necrosis**, ultimately promoting cell growth and inhibiting cell death.

As an anti-aging agent, spermidine suppresses histone acetylation. Moreover, spermidine regulates lipid metabolism. On the one hand, it promotes the differentiation of preadipocytes into mature adipocytes. On the other hand, it alters lipid profile, modulates lipogenic gene expressions, and represses lipid accumulation. Furthermore, spermidine can delay aging through specific signaling pathways, such as SIRT1/PGC-1α, insulin/ IGF, AMPK-FOXO3a, and CK2/MAPK signaling pathways.

Fishoil, EPA, DHA

Fish oil

Fish oil is oil derived from the tissues of oily fish. Fish oils contain the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, precursors of certain eicosanoids that are known to reduce inflammation in the body and improve hypertriglyceridemia. Wikipedia



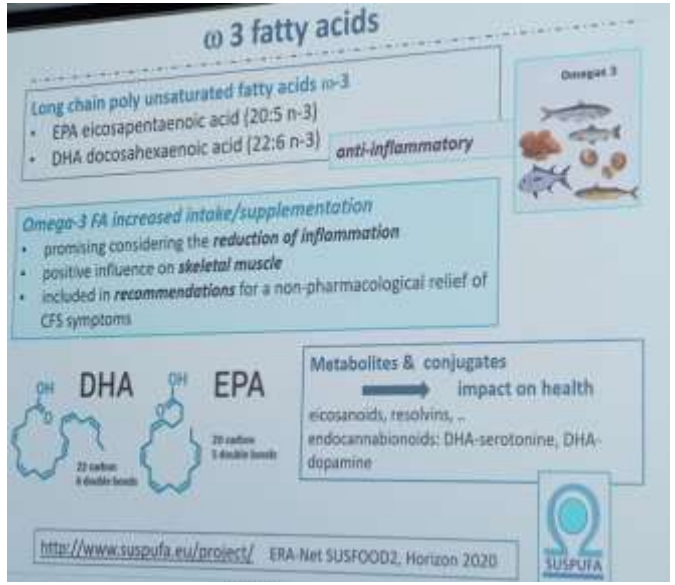
Fishoil II

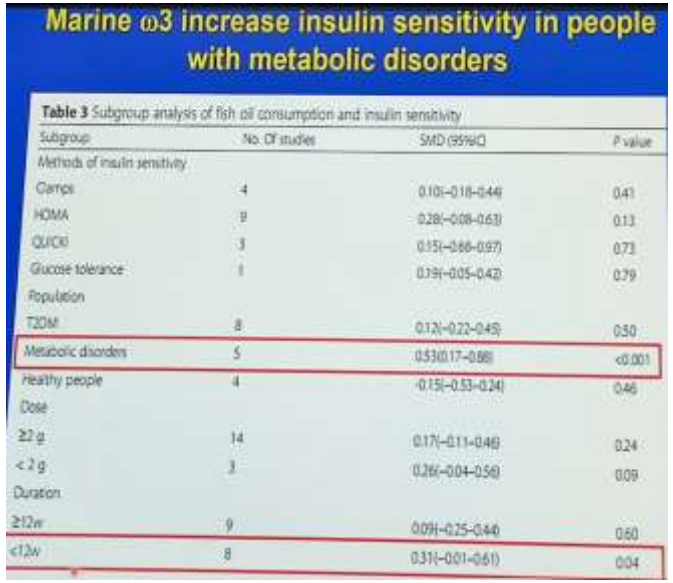
Conclusion

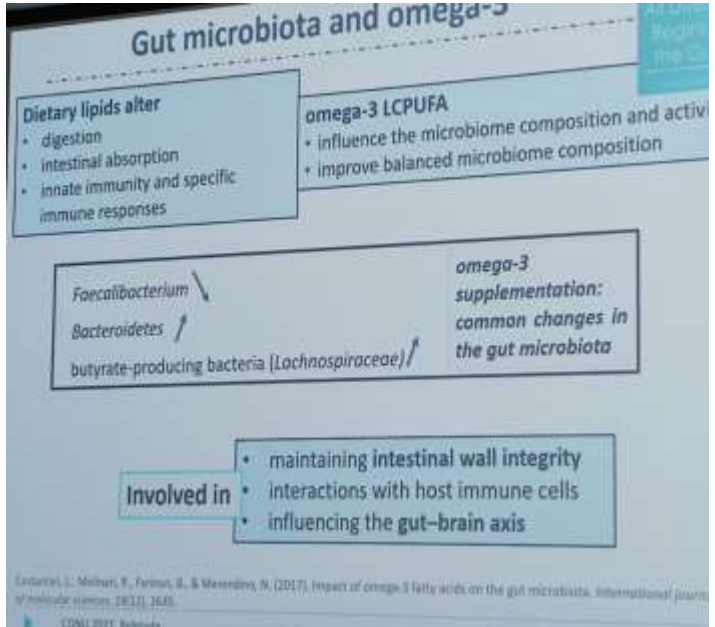
- Quite less ambiguity persists about a true place for marine ω3 to prevent IR
- In healthy humans, 1.8 g/d modestly increase insulin sensitivity
- But 850 mg/d aggravate dexamethasone-induced IR
- The most recent and complete meta-analysis conclude to their preventive effect towards IR
- 4 Meta-analysis conclude to a protective effect in Asian but potentially deleterious in Western populations towards the risk of T2D, probably due to the heterogeneity of western studies and a high n-6/n-3 ratio in western populations

Marine ω3 are certainly useful useful if given early and throughout life cycle, probably at least > 1g/d in adults AND in combination with exercise and maintenance of normal weight.

Personalized dosage should also be considered, which requires further studies



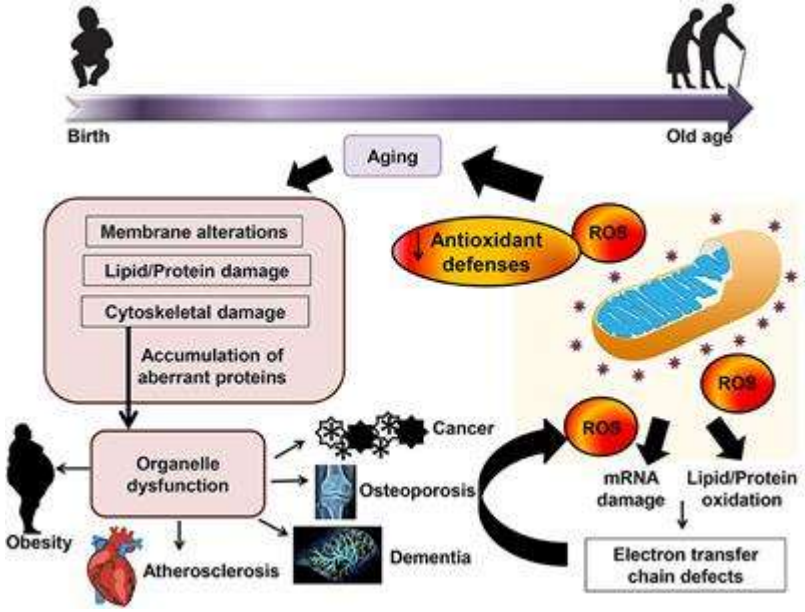


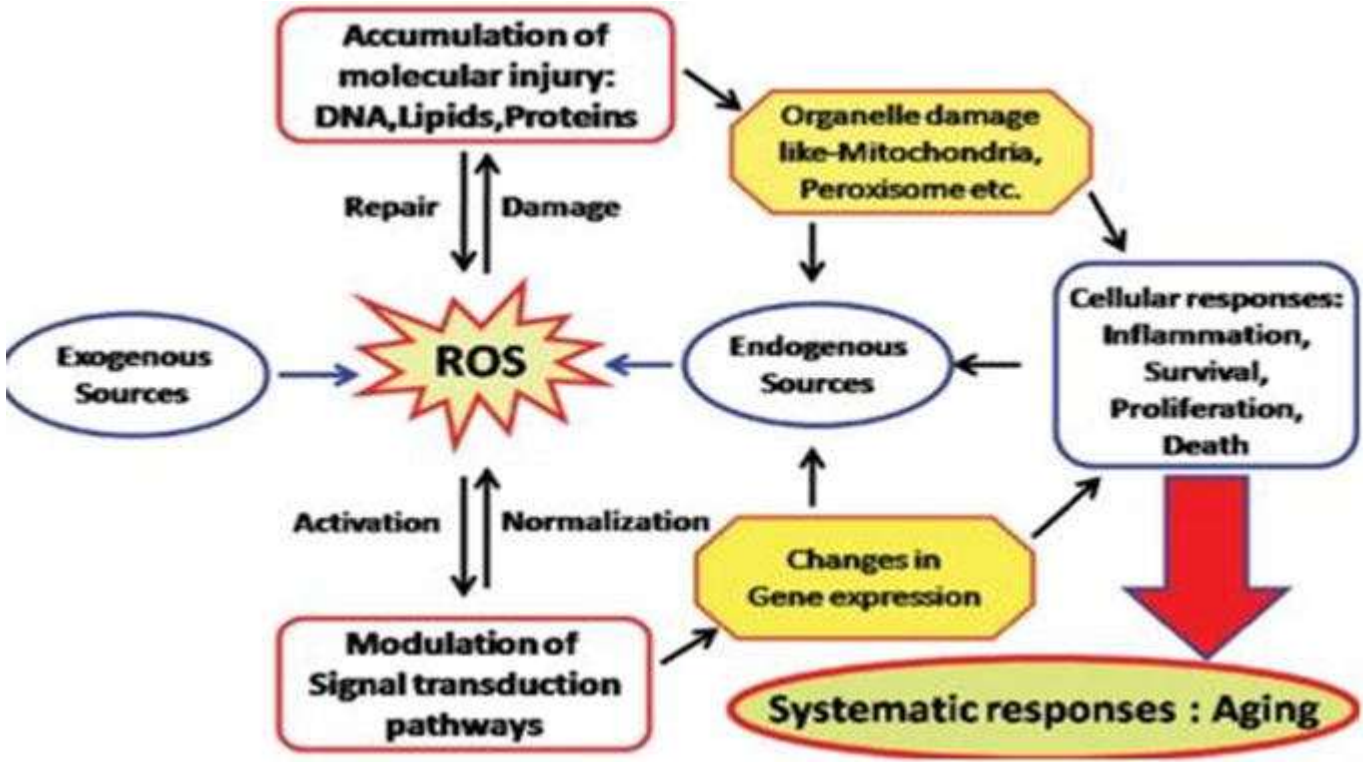


Discussed activities of nutraceuticals along the hallmarks of aging, facts, hypothesis, fiction ?

Anti oxydative	Epigenetic active
inflammation	neuroinflammation
Telomers	Mitochondria
Autophagy	Apoptose
Senolytic	DNa repair
Immune senescence	Nuro infl
Anti bacterial	Anti viral
AGING	

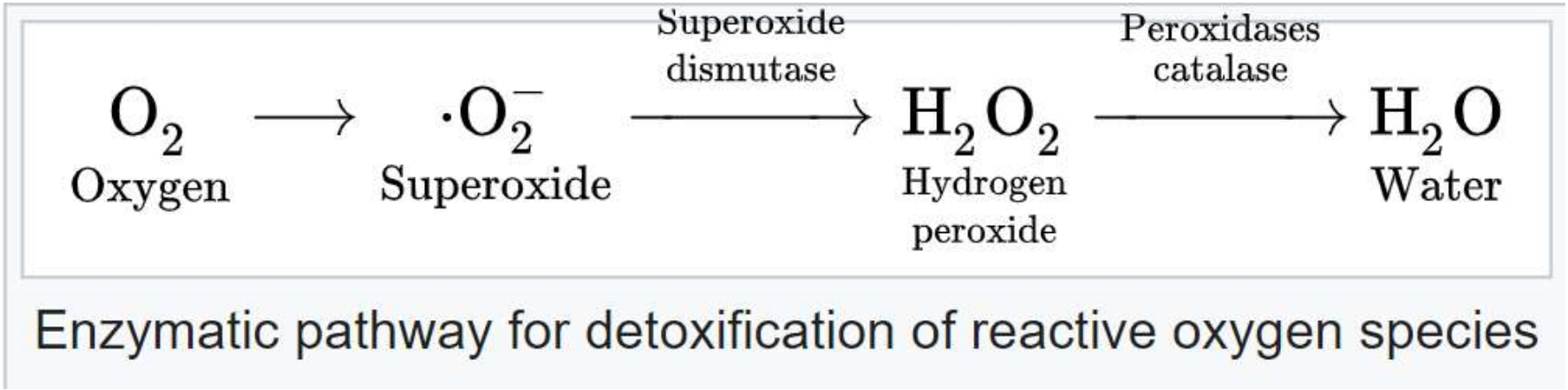
ROS and antioxydative activities





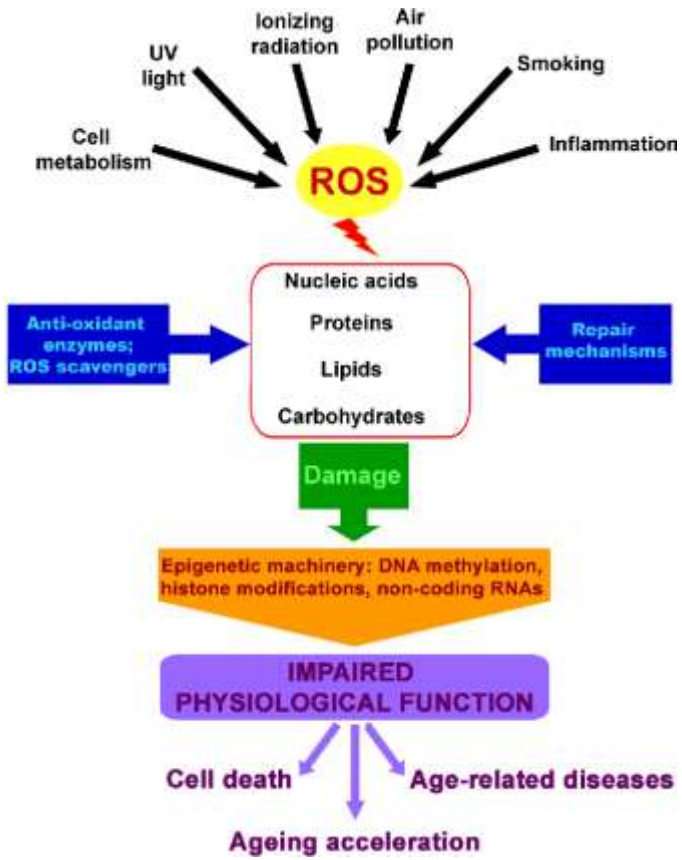
Antioxydants

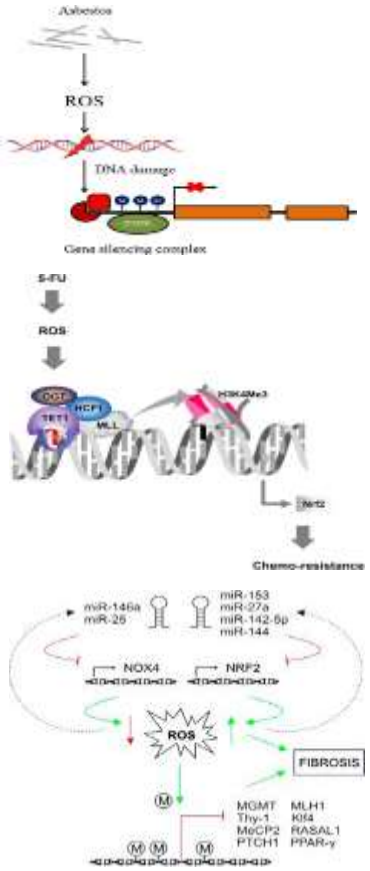
Antioxidant	Solubility	Concentration in human serum (μM)	Concentration in liver tissue (μmol/kg)
Ascorbic acid (vitamin C)	Water	50–60[53]	260 (human)[54]
Glutathione	Water	4[55]	6,400 (human)[54]
Lipoic acid	Water	0.1–0.7[56]	4–5 (rat)[57]
Uric acid	Water	200–400[58]	1,600 (human)[54]
Carotenes	Lipid	β-carotene: 0.5–1[59] retinol (vitamin A): 1–3[60]	5 (human, total carotenoids)[61]
α-Tocopherol (vitamin E)	Lipid	10–40[60]	50 (human)[54]
Ubiquinol (coenzyme Q)	Lipid	5[62]	200 (human)[63]



Enzymatic pathway for detoxification of reactive oxygen species

Ros, stress impairs all mechanisms of the epigenetic machinery - > **aging**





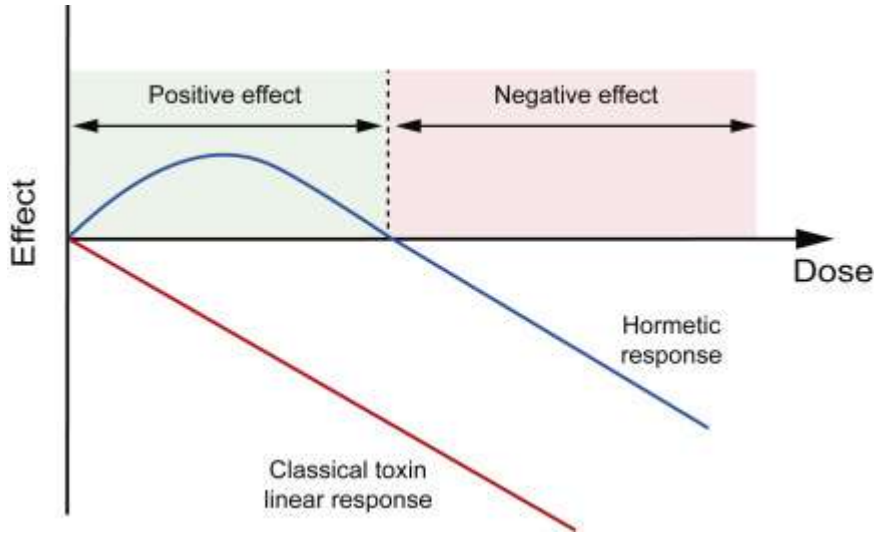
Promotor CpG methylation

Histones

DNA - packaging

Non-coding miRNAs

Stress and Mitormesis



ECG and EGCG are considered antioxidants, which means they counteract or prevent oxidative stress in the body caused by aggressive free radicals of oxygen," said senior co-author Professor Michael Ristow, a researcher in the Department of Health Sciences and Technology at ETH Zurich and the Department of Human Nutrition at the Friedrich Schiller University Jena, and his colleagues.
"Until now, it was assumed that these catechins neutralize free radicals and thus prevent damage to cells or DNA."
"One source of oxygen free radicals is metabolism; for example, when the mitochondria — the powerhouses of the cell — are working to produce energy."
"We took a closer look at how catechins act in the nematode worm *Caenorhabditis elegans* and came to a different, seemingly paradoxical conclusion: rather than suppressing oxidative stress, green tea catechins promote it."
In their experiments, the researchers found that applying the green tea catechins EGCG and ECG at a low dose extends the lifespan of *Caenorhabditis elegans*.
The long-term effects also included reduced fat content in the nematodes after 5 days of catechin treatment.
"ECG and EGCG initially increase oxidative stress in the short term, but that this has the subsequent effect of increasing the defensive capabilities of the cells and the organism," they explained.

Antioxydants, mithormesis

Antioxidants

S. Stanner, E. Weichselbaum

Show more

+ Add to Mendeley Share Cite

https://doi.org/10.1016/B978-0-12-375083-9.00013-1 Get rights and content

Abstract

Antioxidants have the ability to scavenge free radicals in the human body and have been suggested to contribute to the protective effect of plant-based foods on diseases such as cardiovascular disease (CVD), cancer, and type 2 diabetes. However, evidence from supplementation studies using various antioxidants, including vitamin C, vitamin E, carotenoids, zinc, or selenium, does not support the hypothesis that antioxidants decrease risk of these diseases. Intervention studies highlight a lack of information on the safety of sustained intakes of moderate to high doses of micronutrient supplements and suggest that long-term harm cannot be ruled out, particularly in smokers.

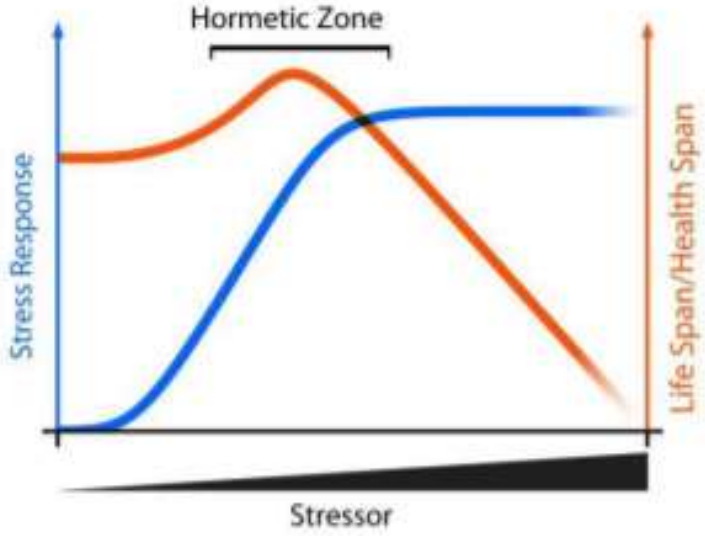
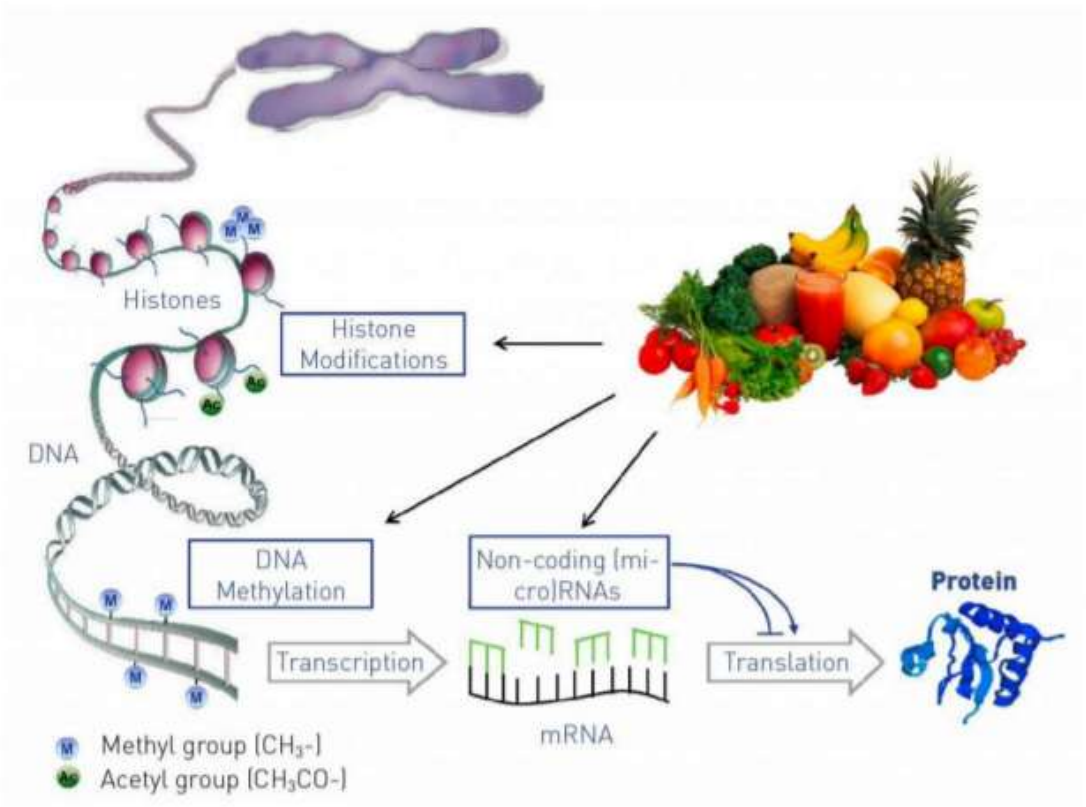


Figure 11. Mithormesis Theoretical curve showing how low doses of a stressor may have beneficial effects by activating intracellular stress response pathways. If the stressor exceeds the capacity of the stress response system to maintain homeostasis, then deleterious phenotypes are observed.

Novel foods, functional foods and epigenetics



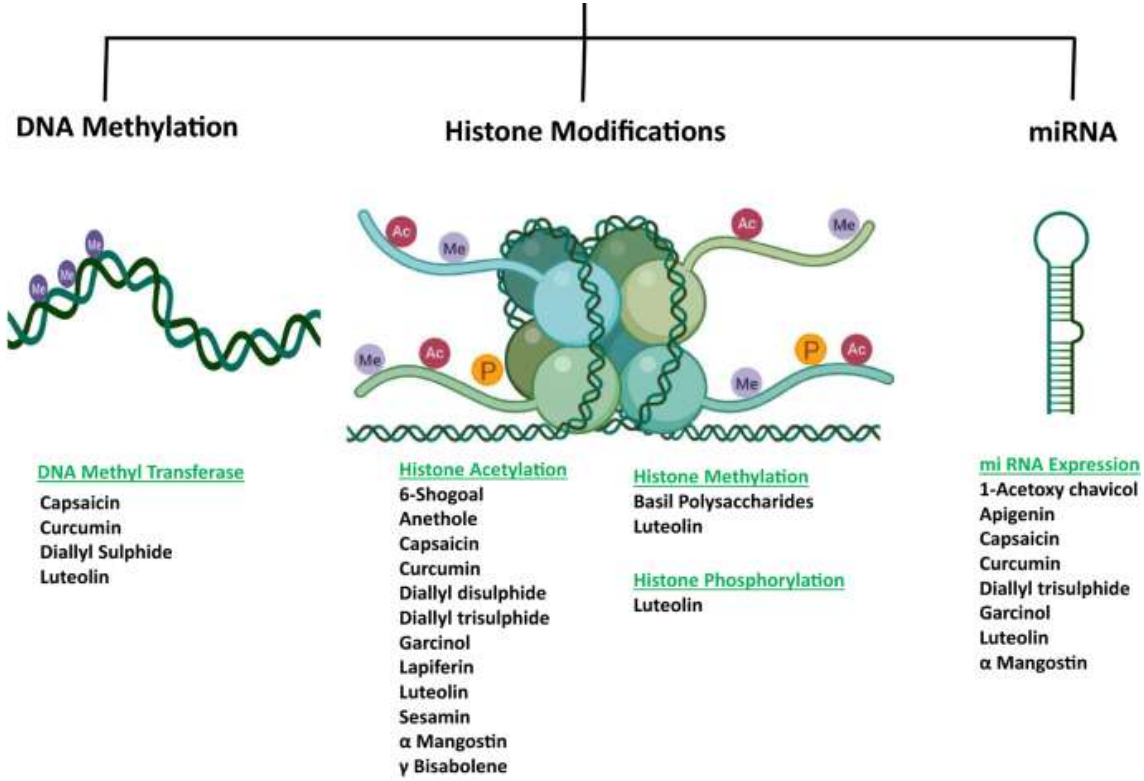
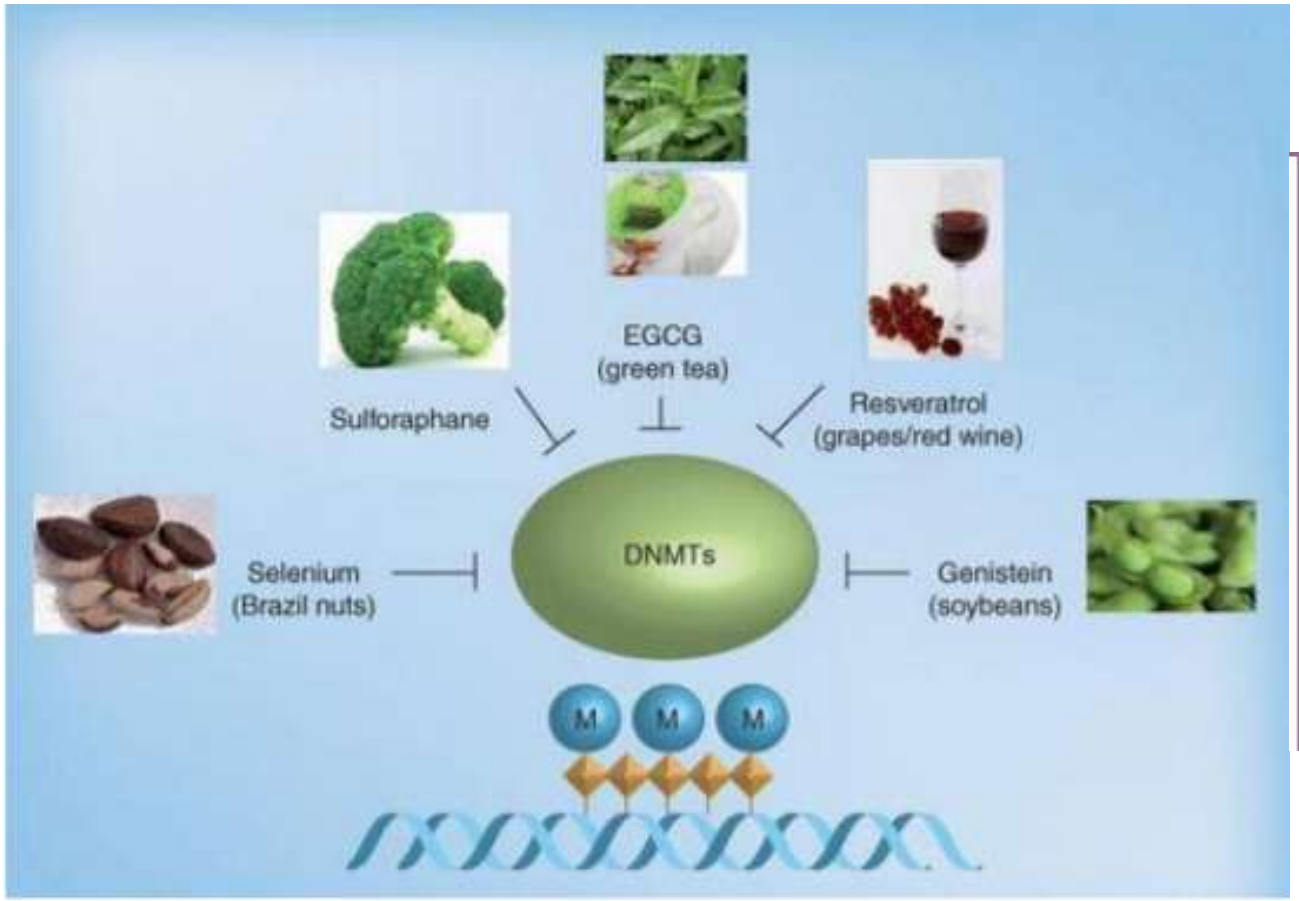
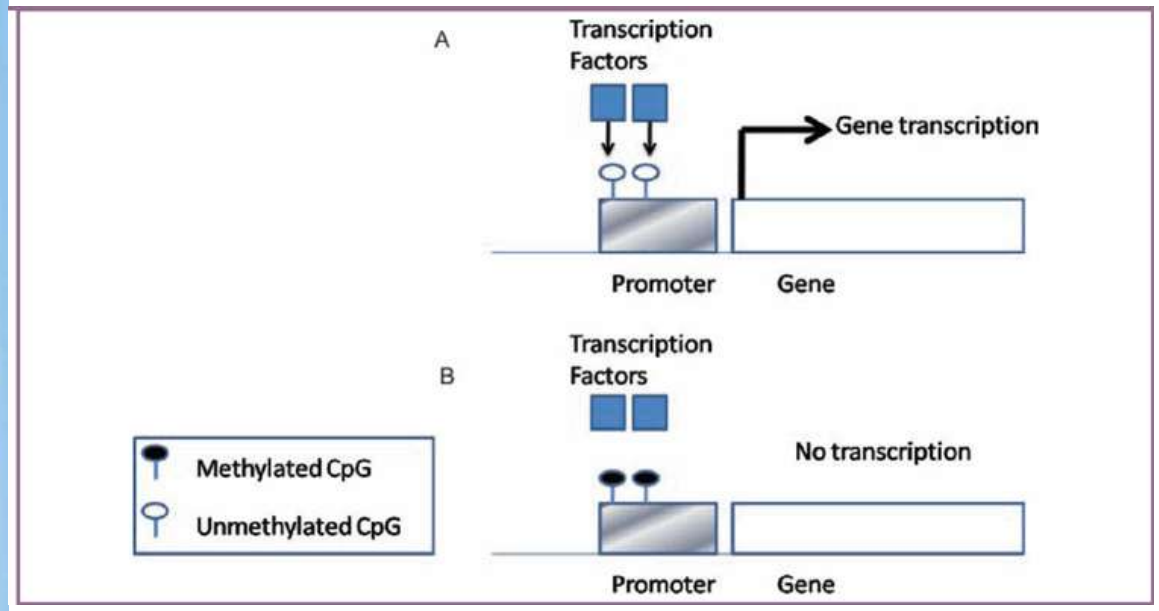


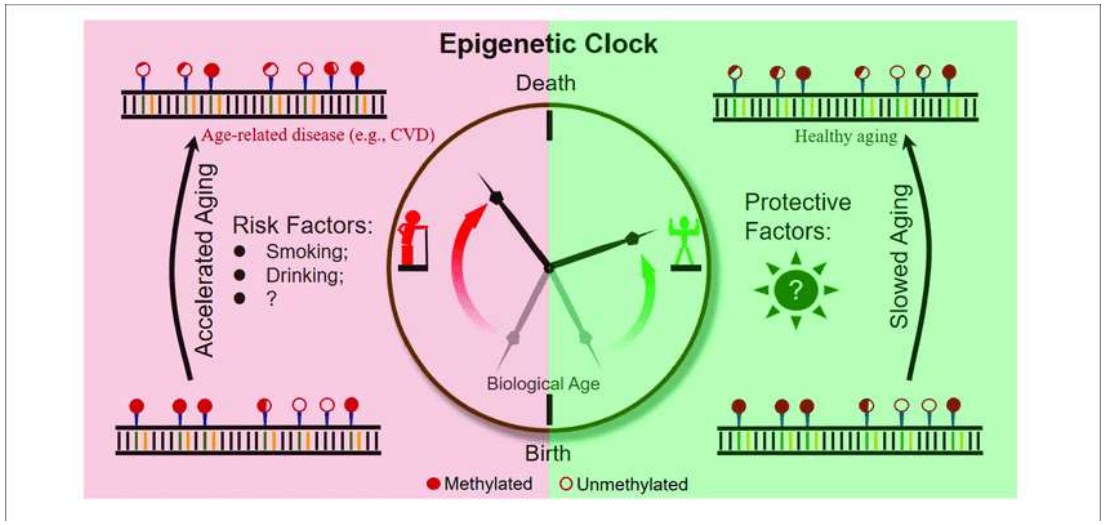
Figure 4. Polyphenols address all epigenetic mechanisms.

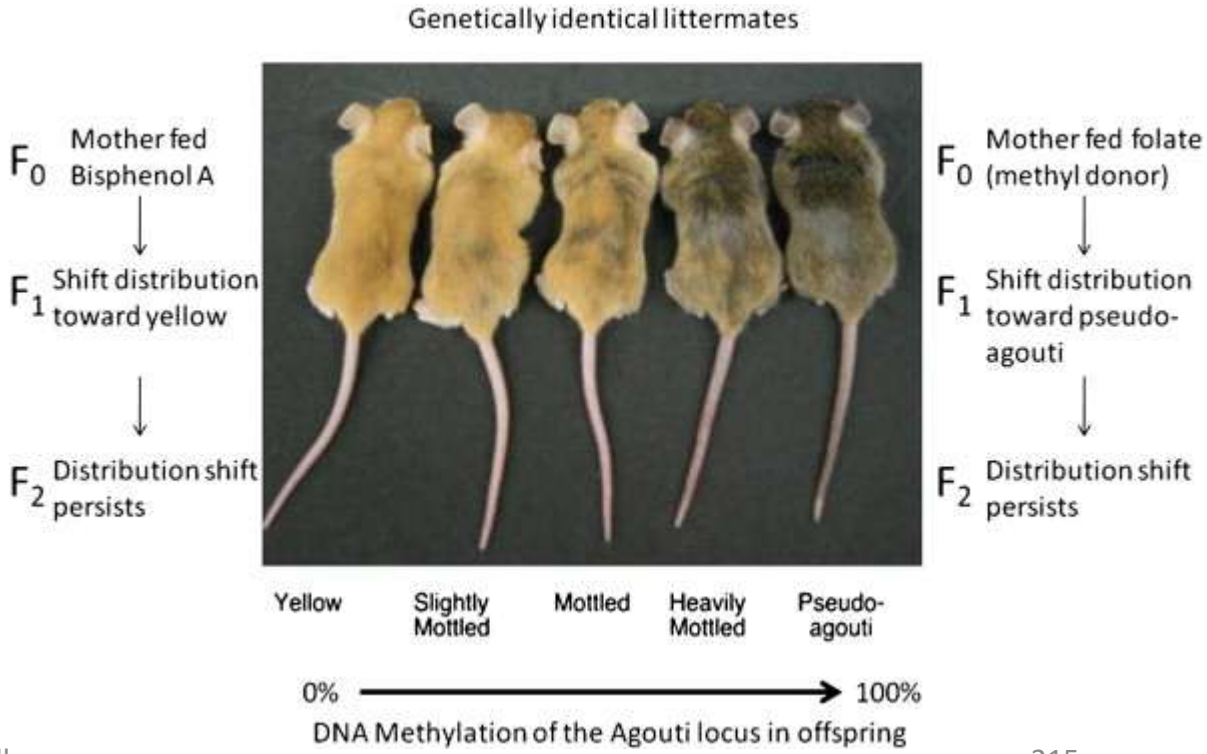
DNA, CpG methylation





Best marker for aging: The epigenetic clock (Horvath) evaluates the biological age, accelerated or decelerated, healthy aging (CpG methylation of 100s of genes)





Effects on histones, chromation

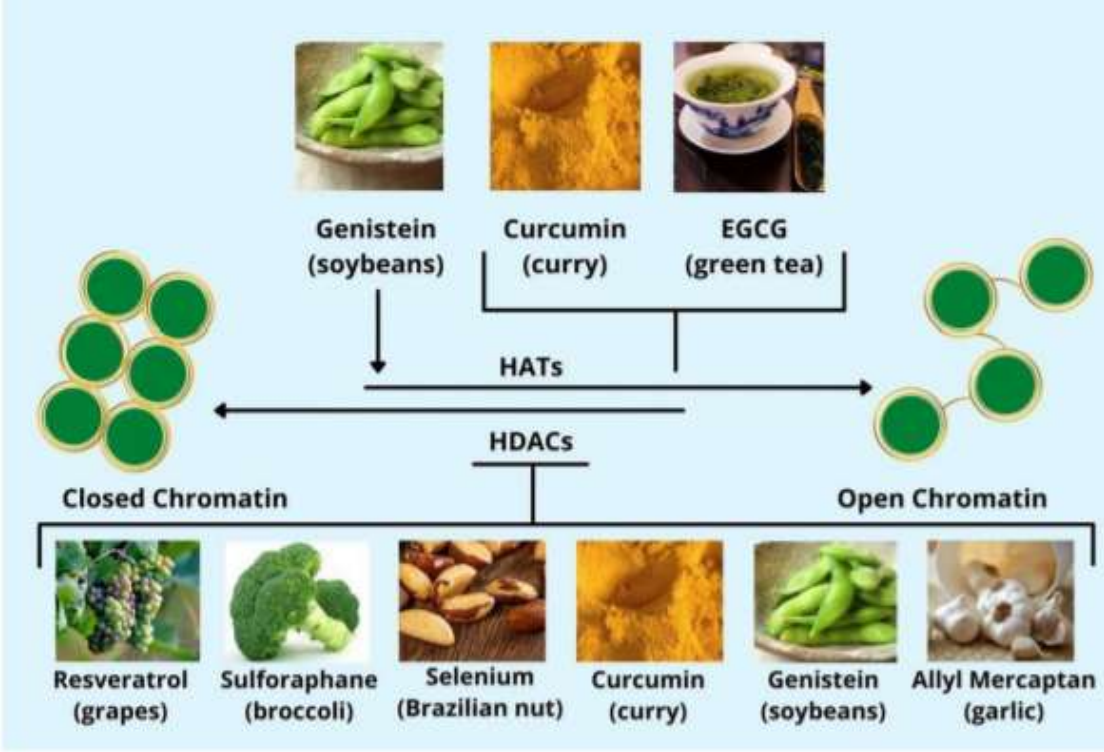


Figure 6. Effects of epigenetic active plant ingredients on histones, chromatin, and gene expression

Sirtuins

Sirtfood	Major Sirtuin-Activating Nutrients
Bird's-eye chilli	Luteolin, Myricetin
Buckwheat	Rutin
Capers	Kaempferol, Quercetin
Celery, including its leaves	Apigenin, Luteolin
Cocoa	Epicatechin
Coffee	Caffeic acid, Chlorogenic acid
Extra virgin olive oil	Oleuropein, Hydroxytyrosol
Green tea (especially matcha green tea)	Epicgallocatechin gallate (EGCG)
Kale	Kaempferol, Quercetin
Lovage	Quercetin
Medjool dates	Gallic acid, Caffeic acid
Parsley	Apigenin, Myricetin
Red chicory	Luteolin
Red onion	Quercetin
Red wine	Resveratrol, Piceatannol
Rocket	Quercetin, Kaempferol
Soy	Daidzein, Formononetin
Strawberries	Fisetin
Turmeric	Curcumin
Walnuts	Gallic acid

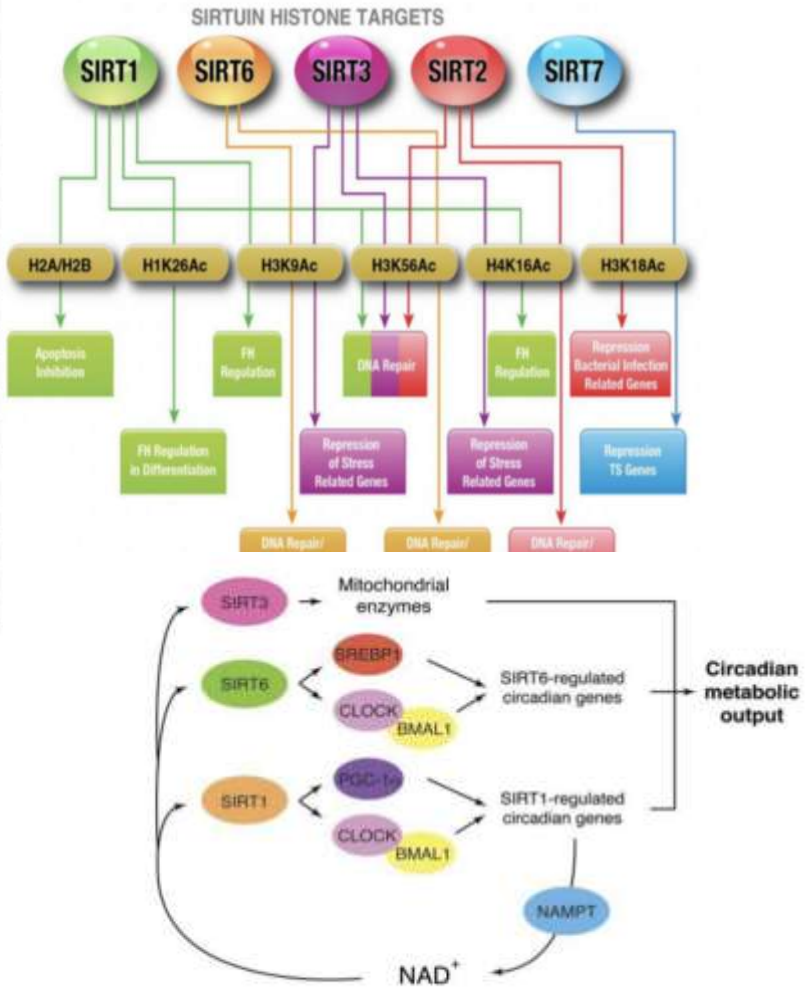


Figure 8. Sirtuins and NAD

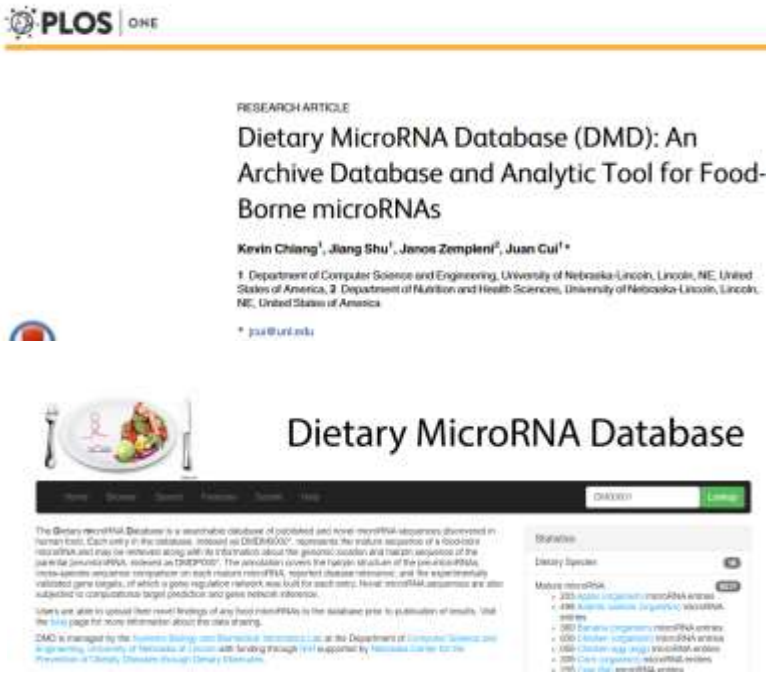
BCHD

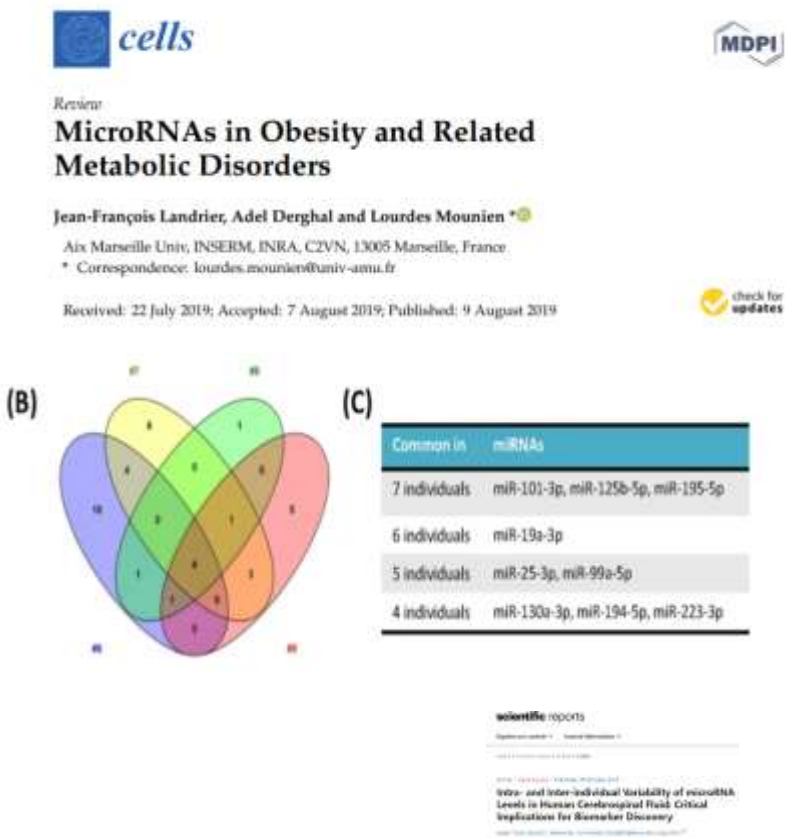
Bioactive Compounds in Health and Disease

Increased Sirtuin expression, senescence regulating miRNAs, mtDNA, and bifidobacteria correlate with wellbeing and skin appearance after Sirtuin- activating drink

Stephanie Lilja, Hanna Bäck, Carinna Stoll, Anna Mayer, Angelika Pointner, Berit Hippe, Ulrike Krammer, Alexander G. Haslberger*

Epigenetic miRNAs: food borne, marker for mechanisms, phenotypes, disorders





Mi RNAS, non coding RNAs

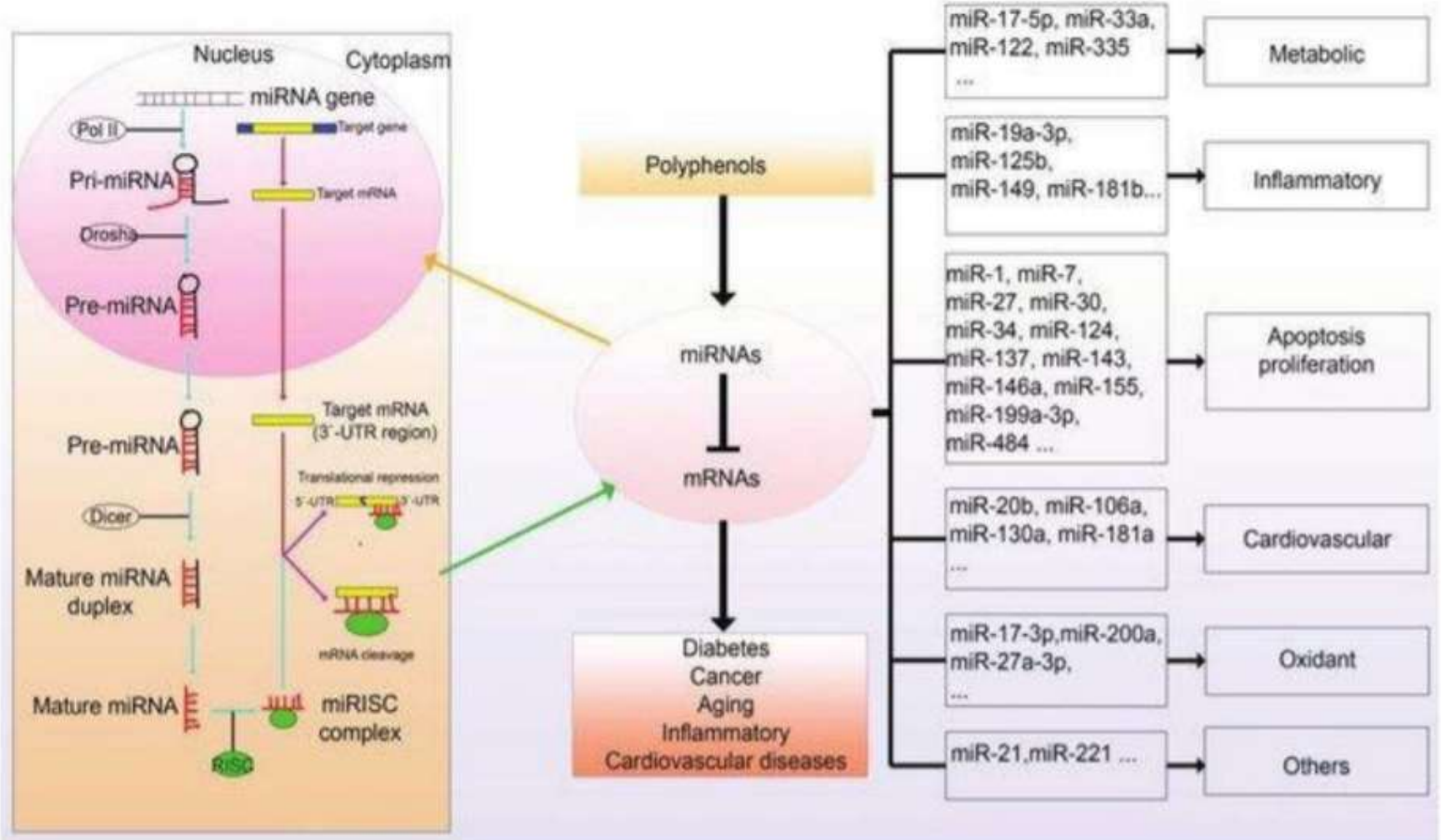
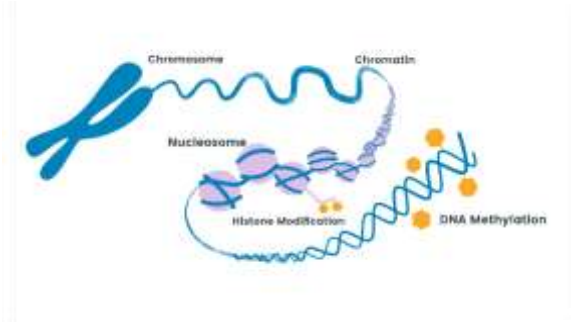
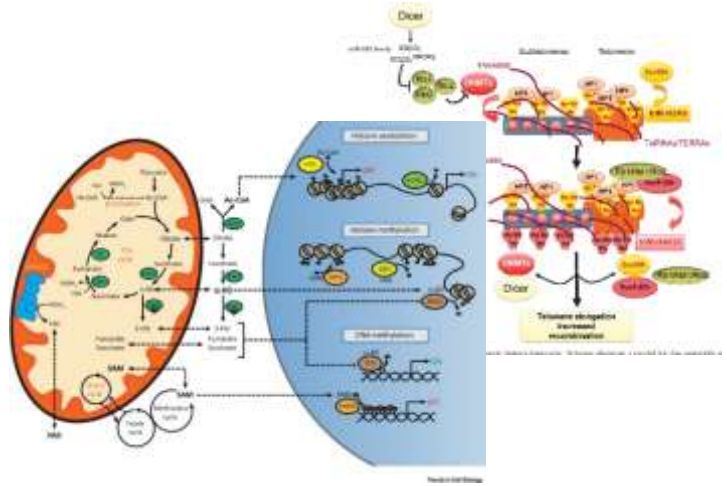
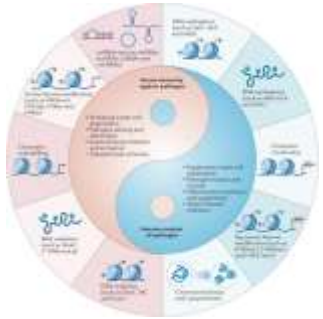


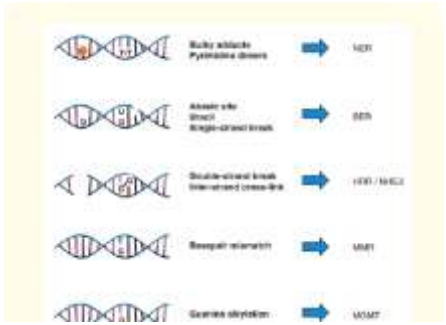
Figure 9. Polyphenols and ncRNAs

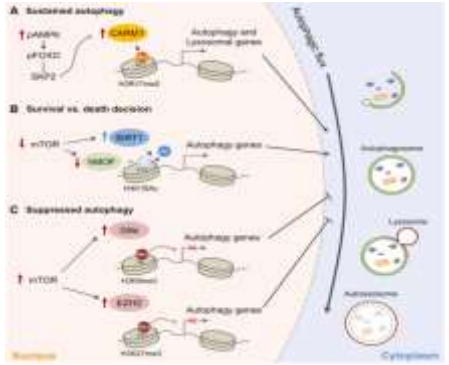
Epigenetics regulates aging mechanisms involved in telomere attrition, mitochondrial functions, autophagy, I.S./inflammation, senescence and DNA-repair



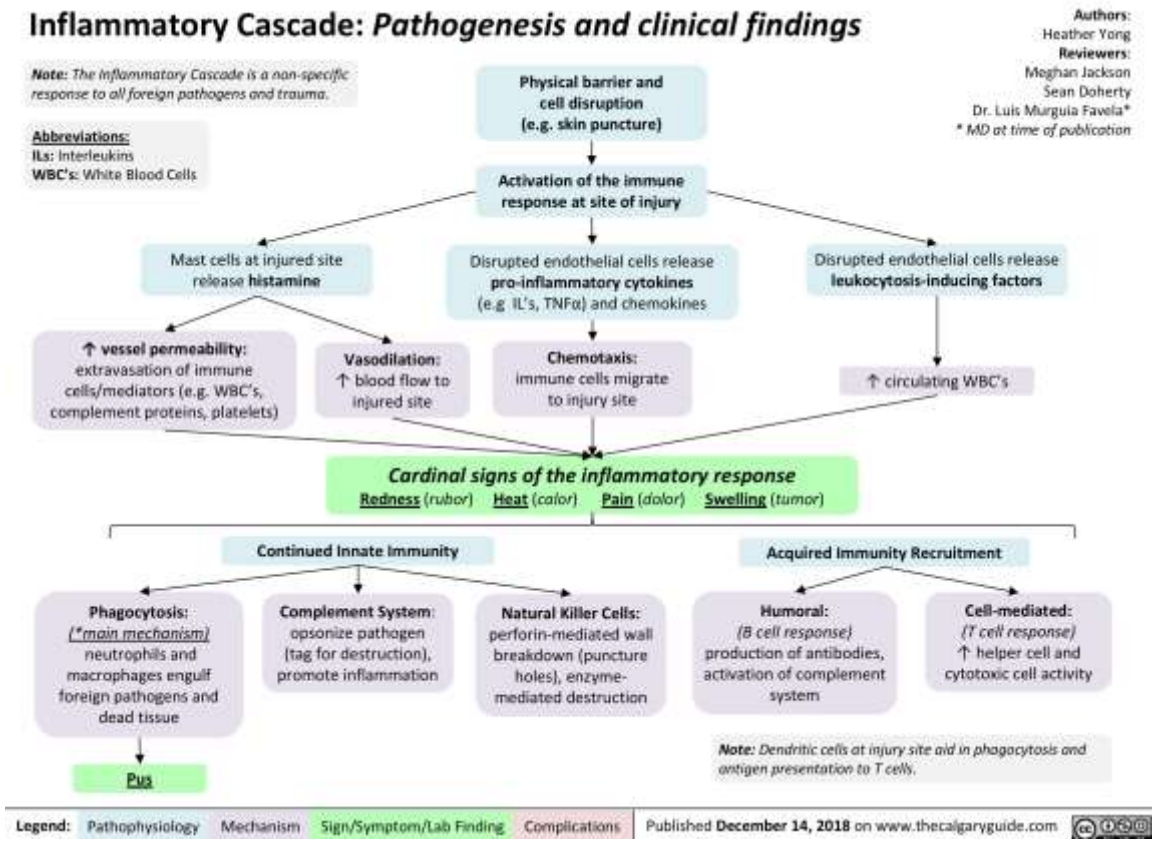


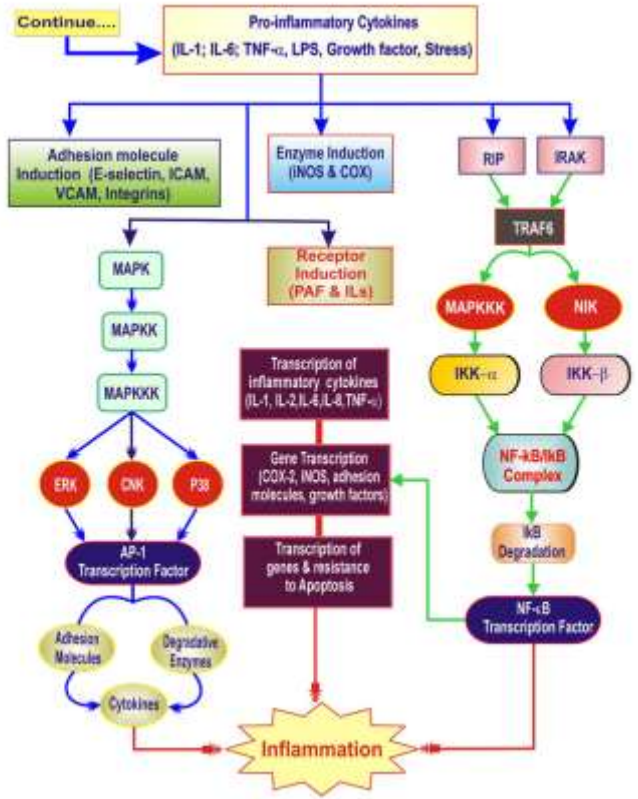




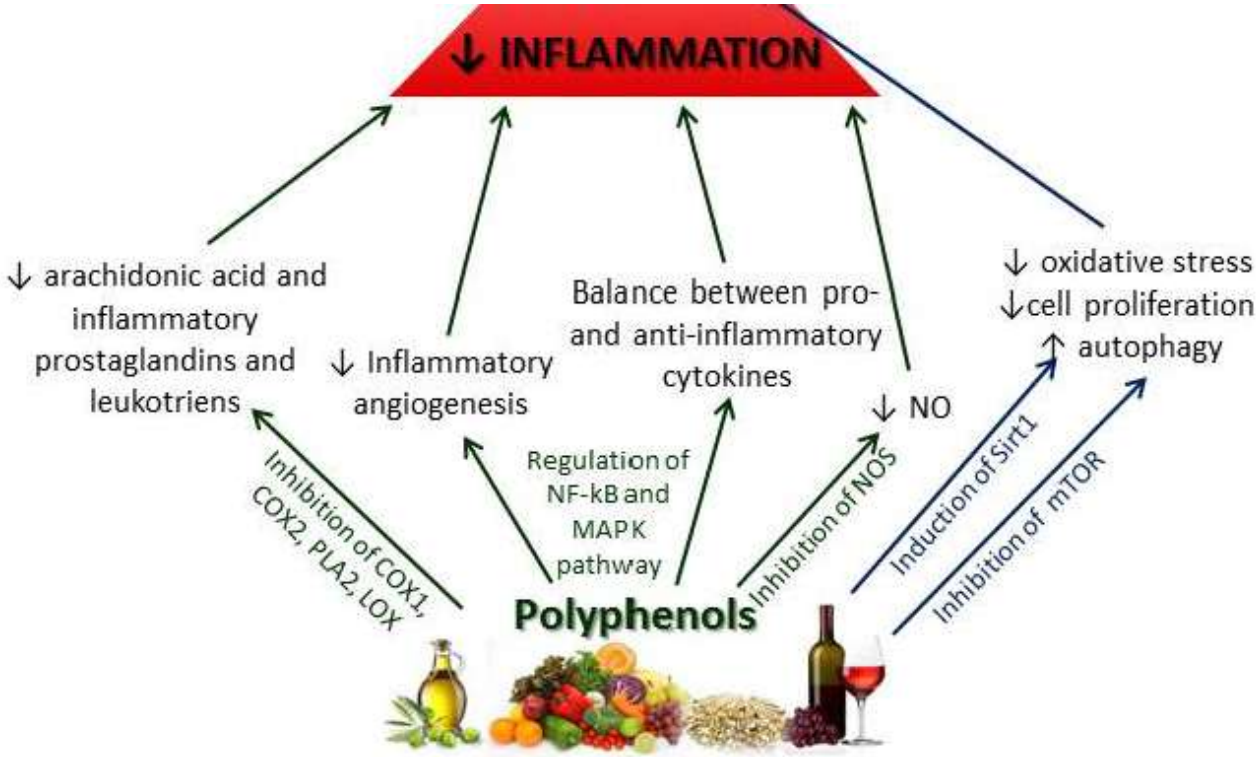


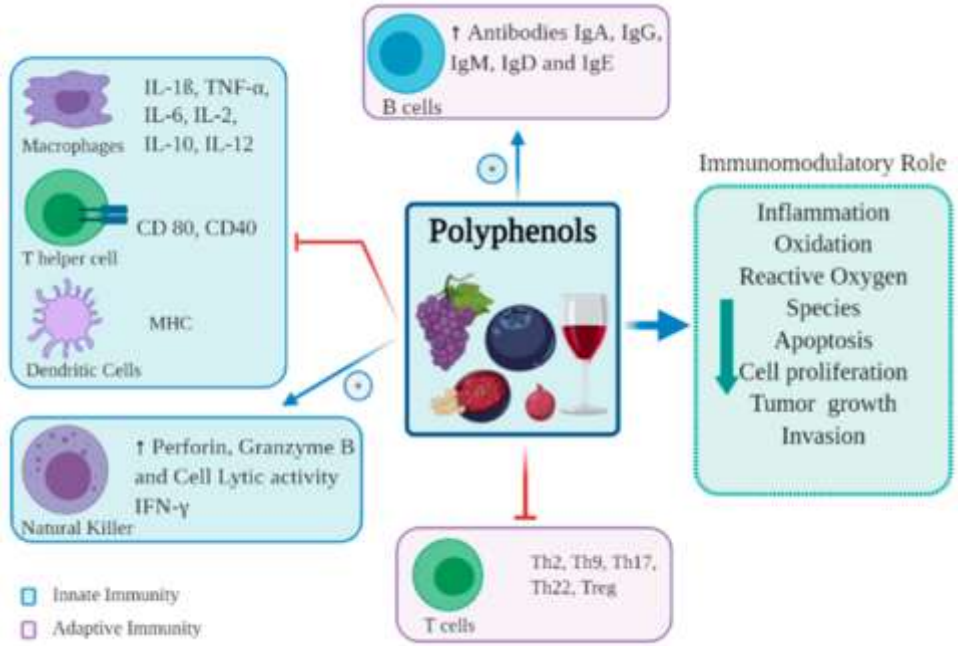
Polyphenols and Inflammation mechanisms





Polyphenol effects inflammation:





Polyphenols and NRF2

The nuclear factor erythroid 2–related factor 2 (Nrf2) is an emerging regulator of cellular resistance to oxidants. Nrf2 controls the basal and induced expression of an array of antioxidant response element–dependent genes to regulate the physiological and pathophysiological outcomes of oxidant exposure.

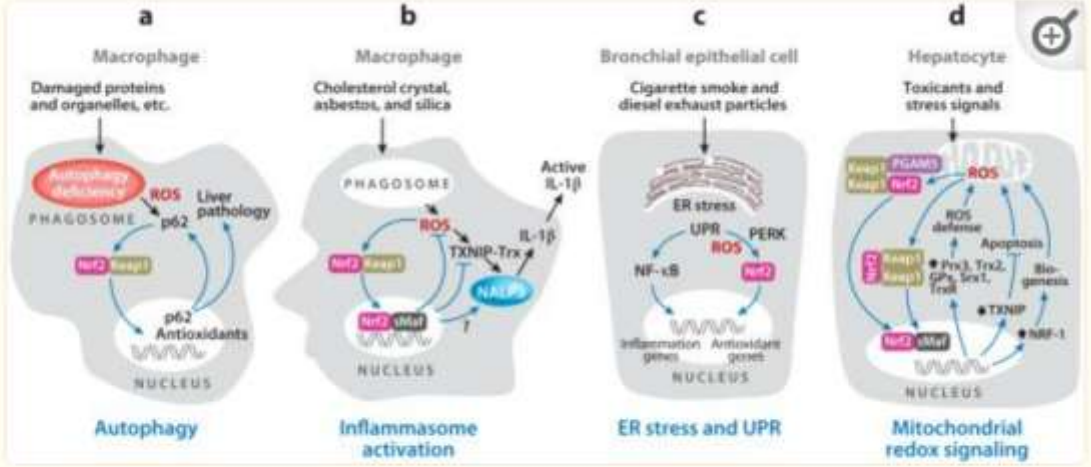
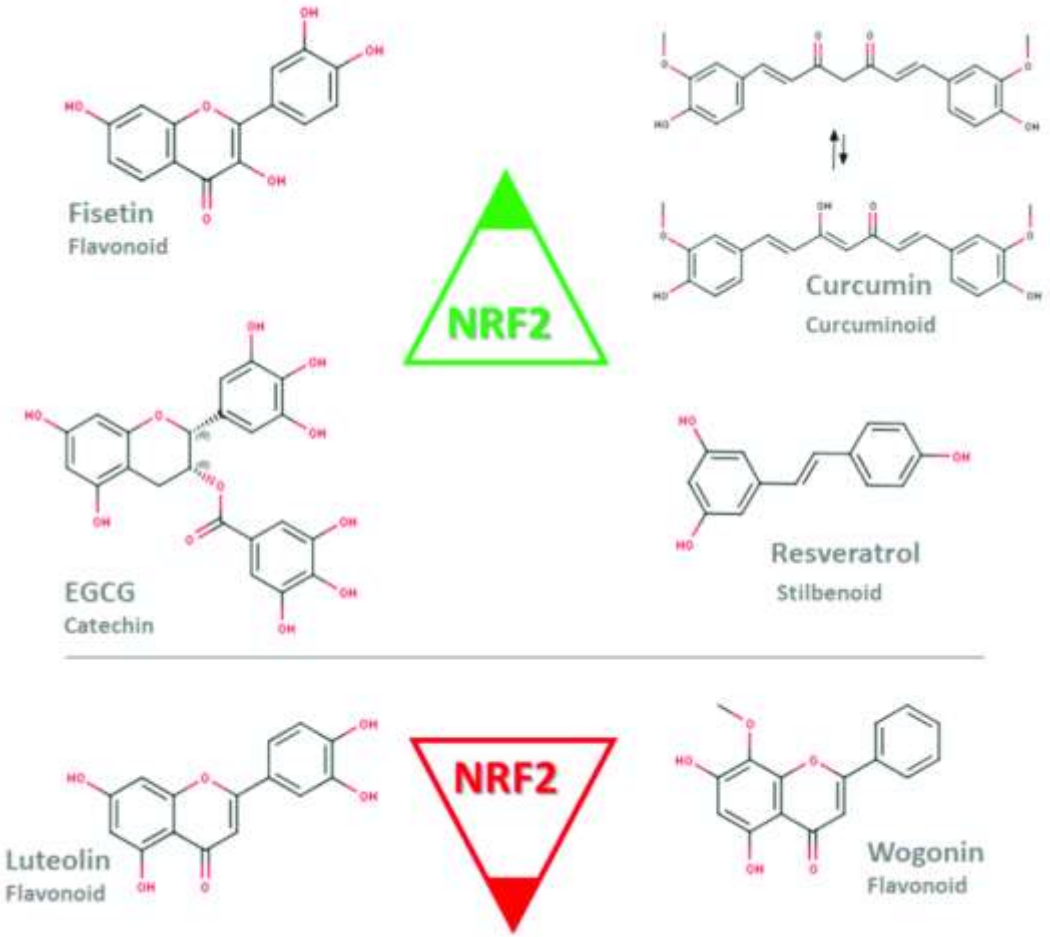


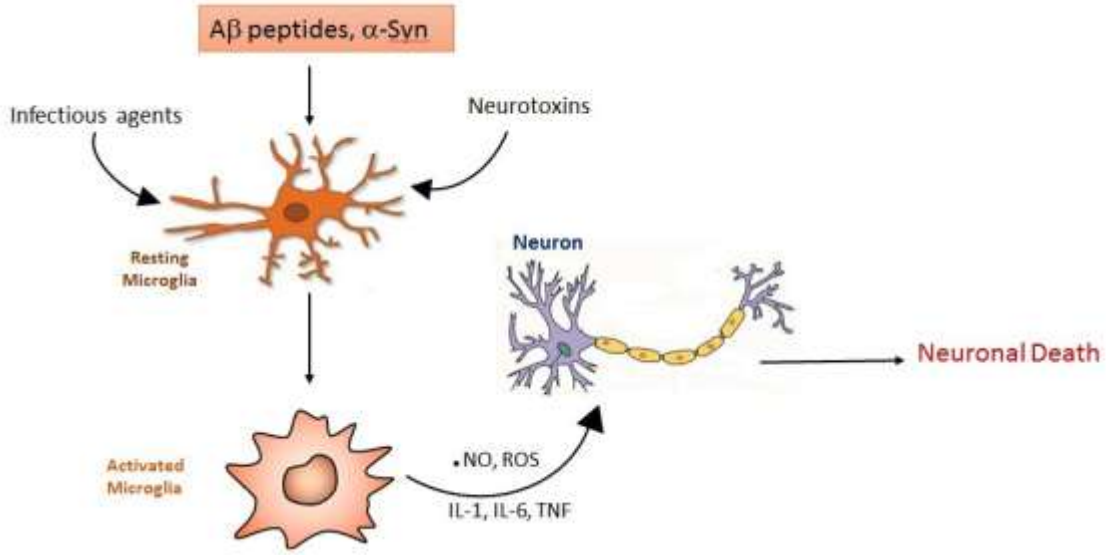
Figure 3

Nrf2 and oxidant-stimulated programmatic functions. (*a*) Autophagy. (*b*) Inflammasome activation. (*c*) Endoplasmic reticulum (ER) stress and unfolded protein response (UPR). (*d*) Mitochondrial redox signaling. Abbreviations: GPx, glutathione peroxidase; Keap1, Kelch-like ECH-associated protein 1; Maf, musculoaponeurotic fibrosarcoma protein; Nrf2, nuclear factor erythroid 2–related factor 2; PERK, protein kinase RNA-like endoplasmic reticulum kinase; Prx, peroxiredoxin; ROS, reactive oxygen species; Srx, sulfiredoxin; Trx, thioredoxin; TrxR, thioredoxin reductase.

NRF2 agonists, antiagonists



Neuro- inflammation



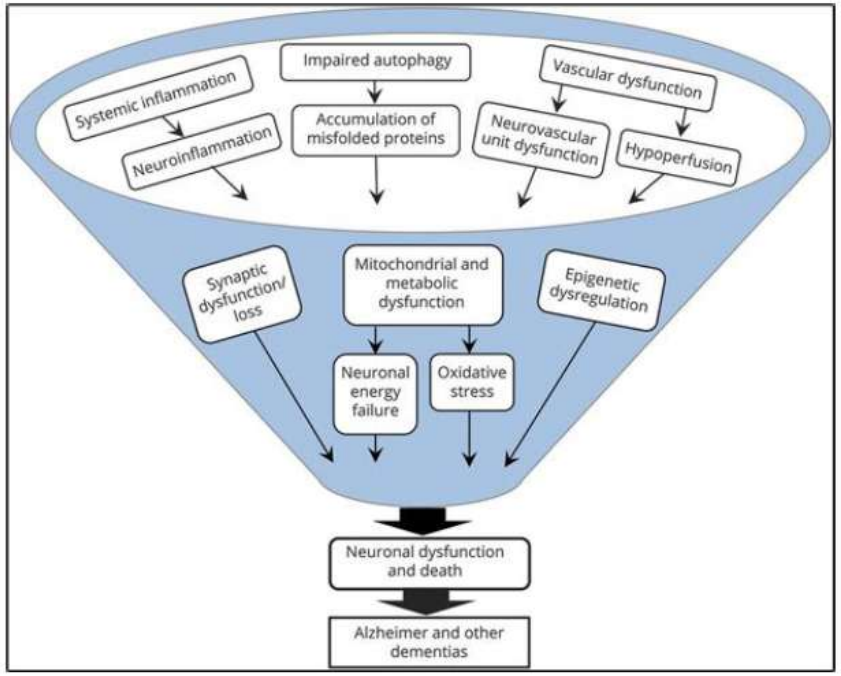
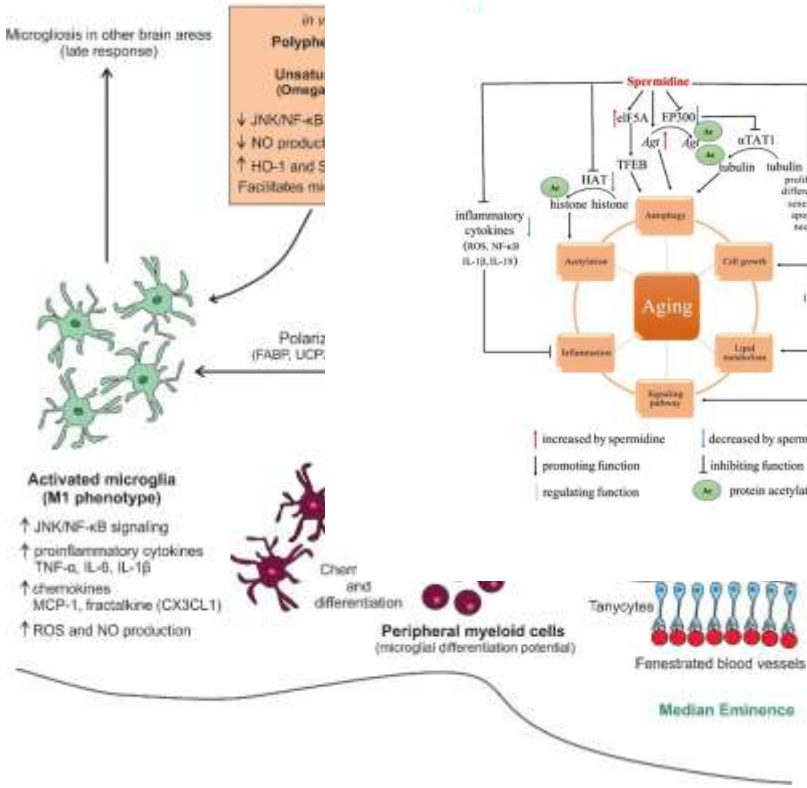


Figure 1. Microglial cells respond differently depending upon type and intensity of activation signals. [17].

Polyphenols, spermidin and microglia



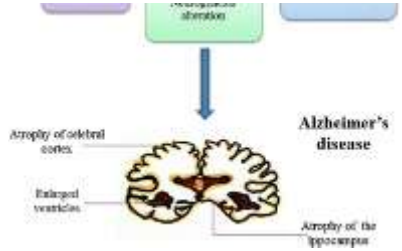
Spermidine mechanisms

Molecular and cellular mechanisms of spermidine in age-related diseases. Spermidine is an inducer of autophagy, which is the main mechanism of anti-aging. First, spermidine **triggers autophagy by modulating the expressions of *Atg* genes**. Second, it regulates **transcription factor eIF 5A to promote the synthesis of transcription factor TFEB.** Third, spermidine **inhibits EP300, which directly promotes the acetylation of Atg genes** and **indirectly stimulates deacetylation of tubulin due to inhibition of aTAT1**. Besides, spermidine exerts potent anti-inflammatory roles by **suppressing of multiple inflammatory cytokines, such as ROS, NF-κB, IL-1β and IL-18**. Moreover, it is involved in regulation **of cell proliferation, differentiation, senescence, apoptosis and necrosis**, ultimately promoting cell growth and inhibiting cell death.
As an anti-aging agent, spermidine suppresses histone acetylation. Moreover, spermidine regulates lipid metabolism. On the one hand, it promotes the differentiation of preadipocytes into mature adipocytes. On the other hand, it alters lipid profile, modulates lipogenic gene expressions, and represses lipid accumulation. Furthermore, spermidine can delay aging through specific signaling pathways, such as SIRT1/PGC-1α, insulin/ IGF, AMPK-FOXO3a, and CK2/MAPK signaling pathways.

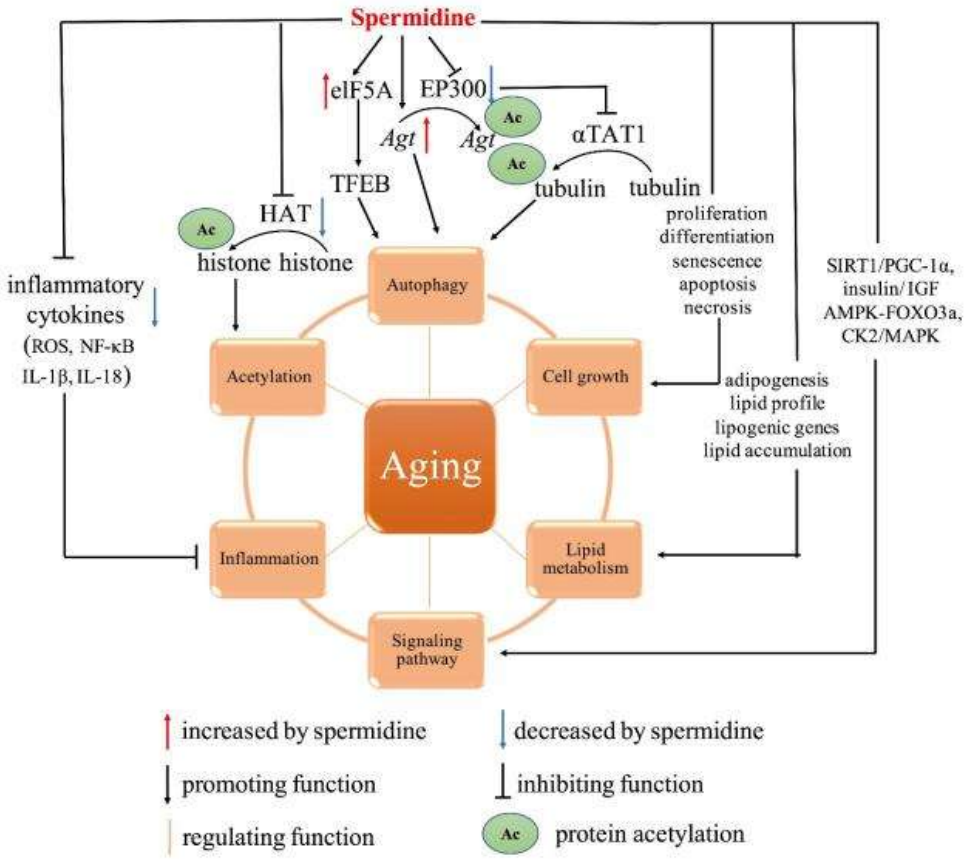
MDPI

Autophagy and
mer's Disease:

Ia Jengic [3,†], Borut Peterlin [4,†] and



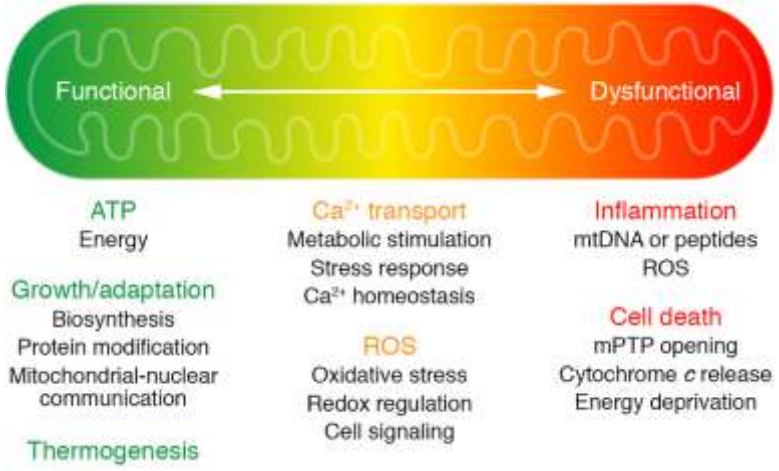
Spermidine mechanisms

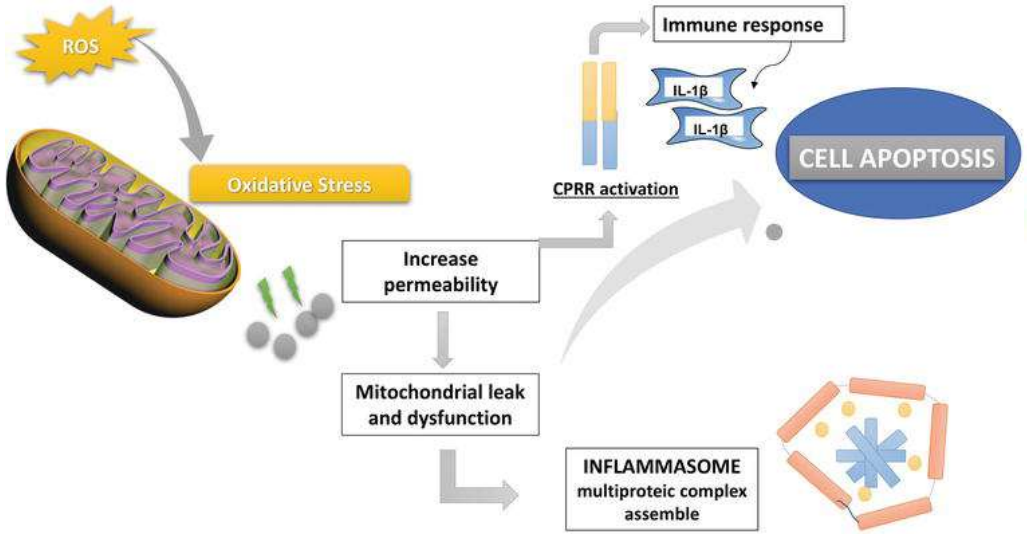


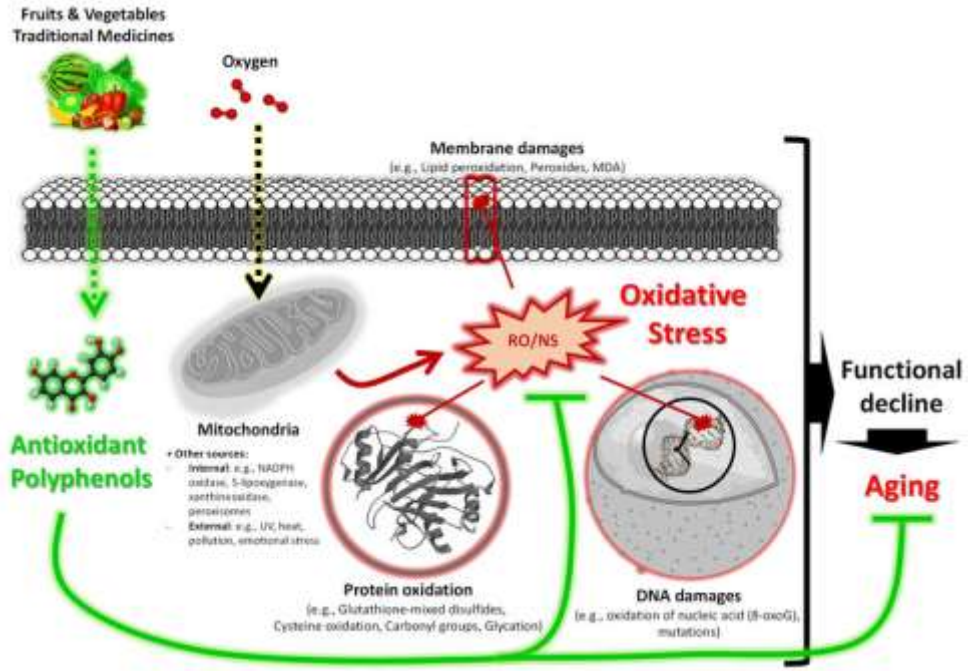
Molecular and cellular mechanisms of spermidine in age-related diseases . Spermidine is an inducer of autophagy, which is the main mechanism of anti-aging. First, spermidine **triggers autophagy by modulating the expre ssions of *Atg* genes**. Second, it regulates **transcription factor eIF5A to pr omote the synthesis of transcription factor TFEB.** Third, spermidine **inhi bits EP300, which directly promotes the acetylation of Atg genes** and **in directly stimulates deacetylation of tubulin due to inhibition of aTAT1**. B esides, spermidine exerts potent anti-inflammatory roles by **suppressing of multiple inflammatory cytokines, such as ROS, NF-κB, IL-1β and IL-18** . Moreover, it is involved in regulation **of cell proliferation, differentiatio n, senescence, apoptosis and necrosis**, ultimately promoting cell growth and inhibiting cell death.

As an anti-aging agent, spermidine suppresses histone acetylation. More over, spermidine regulates lipid metabolism. On the one hand, it promot es the differentiation of preadipocytes into mature adipocytes. On the ot her hand, it alters lipid profile, modulates lipogenic gene expressions, an d represses lipid accumulation. Furthermore, spermidine can delay aging through specific signaling pathways, such as SIRT1/PGC-1α, insulin/ IGF, A MPK-FOXO3a, and CK2/MAPK signaling pathways.

Polyphenols and mitochondria, the oldest theory of aging







Mitochondria directed EGCG protects from H2O2 induced cell apoptosis

RSC Advances

PAPER

View Article Online

Check for updates

Cite this: RSC Adv., 2023, 13, 29477

Mitochondria-targeting EGCG derivatives protect H9c2 cardiomyocytes from H_2O_2-induced apoptosis: design, synthesis and biological evaluation†

Revathy Sahadevan,‡[a] Anupama Binoy,‡[b] Irene Shajan[a]

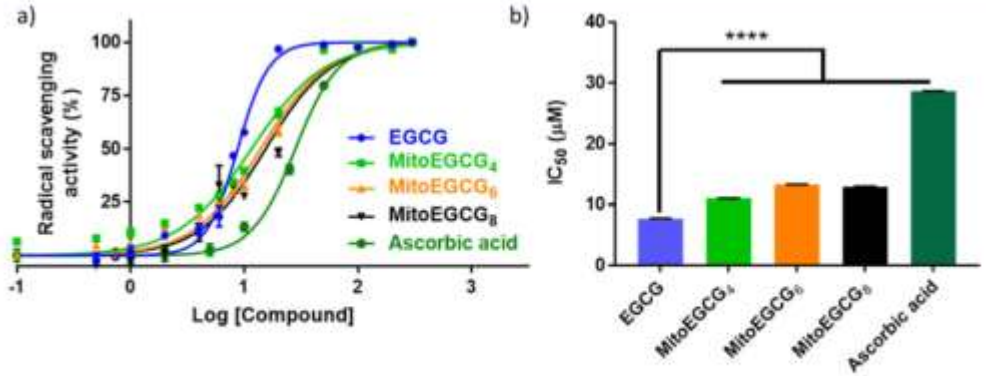


Fig. 1 (a) *In vitro* antioxidant profiles of EGCG, MitoEGCG$_4$, MitoEGCG$_6$, MitoEGCG$_8$ and ascorbic acid as derived from DPPH assay, (b) comparison and evaluation of IC_{50} values of EGCG, MitoEGCG$_4$, MitoEGCG$_6$, MitoEGCG$_8$ and ascorbic acid obtained from DPPH assay. Data are expressed as mean ± standard error of the mean (SEM) and **** represents $p < 0.0001$.

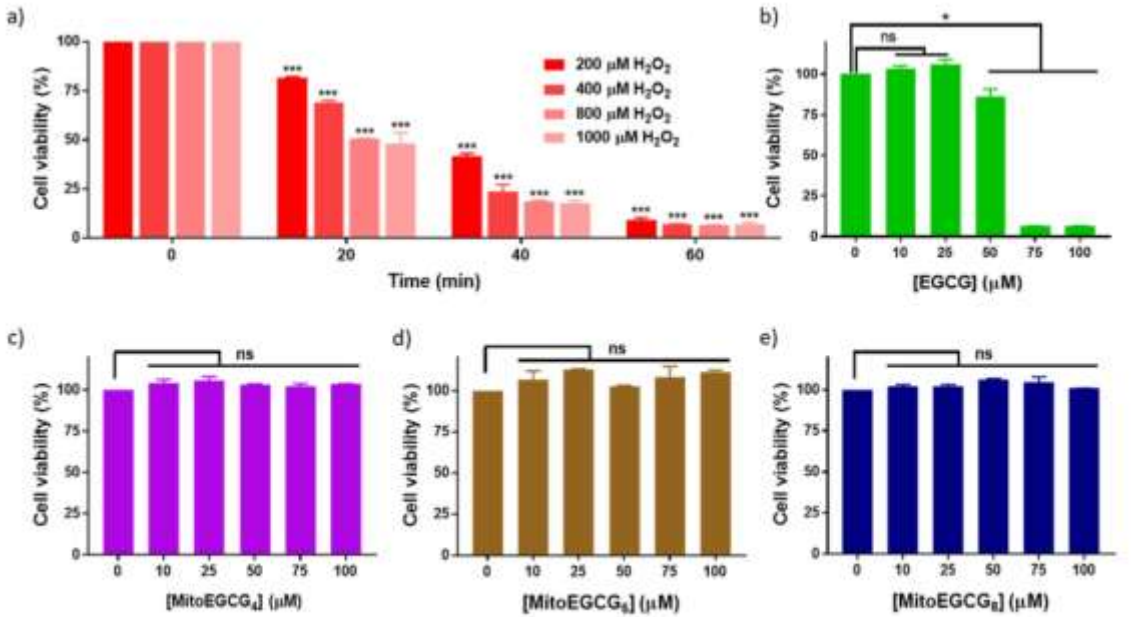
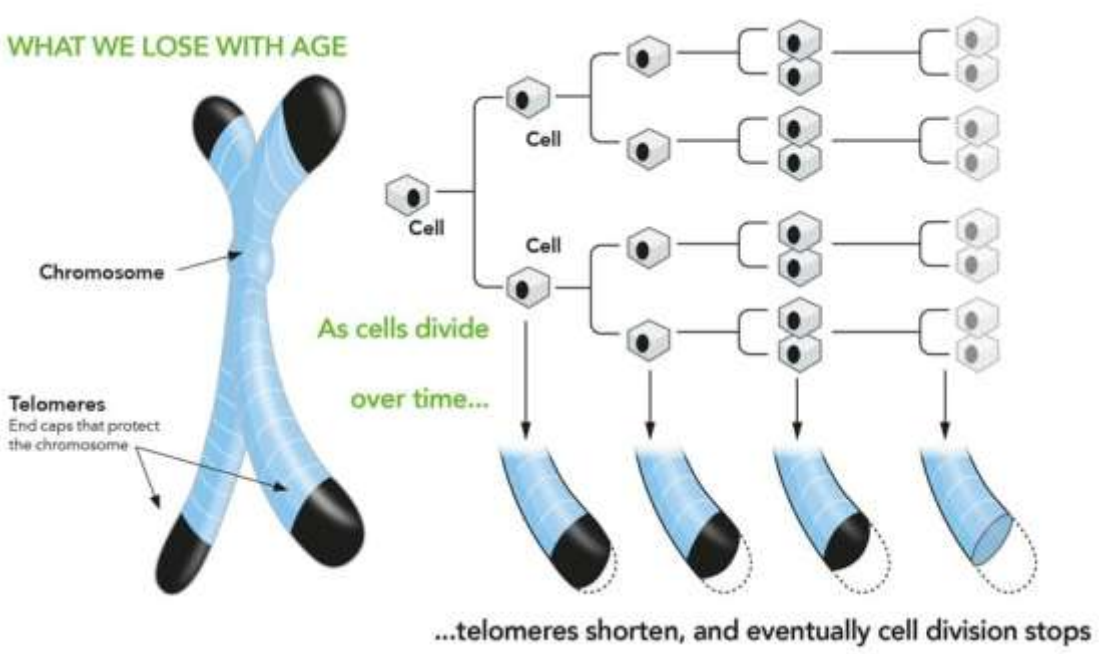
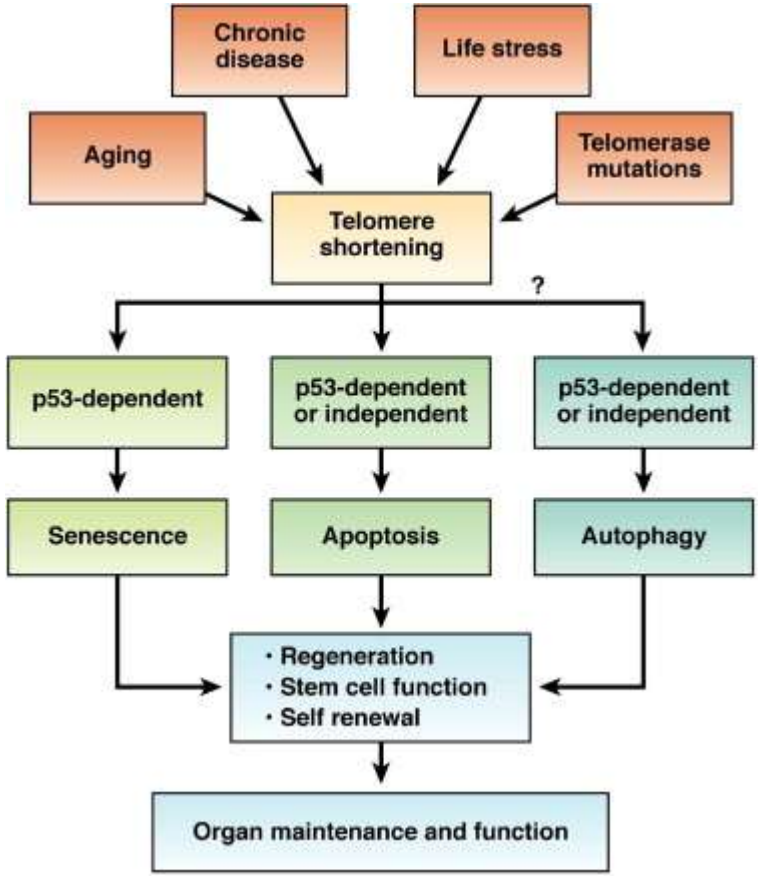


Fig. 2 Cell viability of H9c2 cells treated with (a) different concentrations of H_2O_2 (0–1000 μM) at different time points (0–60 min), (b) EGCG for 24 h, (c) MitoEGCG$_4$ for 24 h, (d) MitoEGCG$_6$ for 24 h and (e) MitoEGCG$_8$ for 24 h. All the experiments have been conducted in triplicates. ***$p <$ 0.001 compared with respective treatment for 0 min, ns denotes $p > 0.05$ (non-significance) and *$p < 0.05$ as compared to DMSO control.

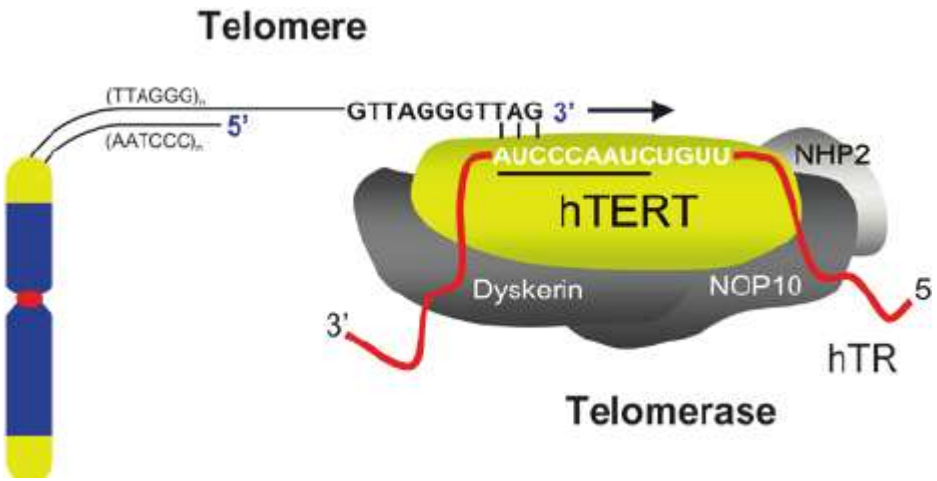
mitochondrial-targeting EGCG derivatives, namely MitoEGCGn (n = 4, 6, 8) by incorporating triphenylphosphonium ion onto it using different linkers.

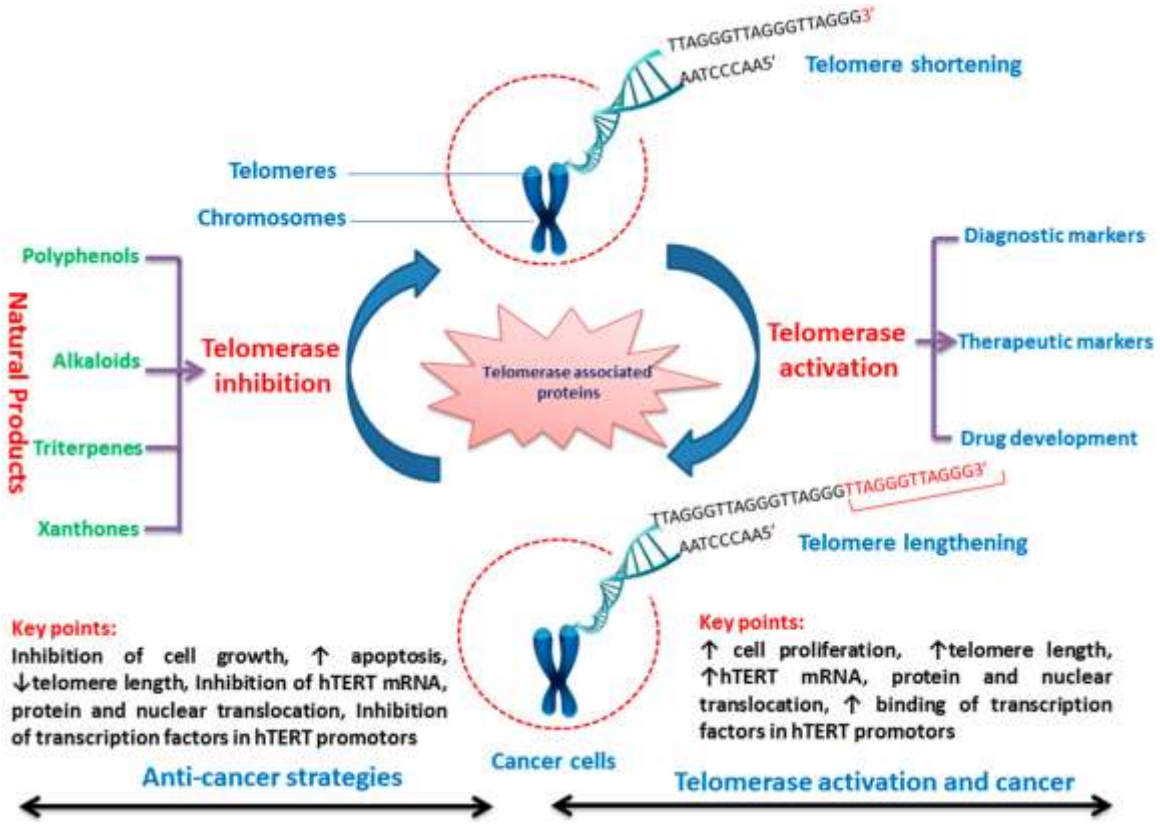
Telomer attrition



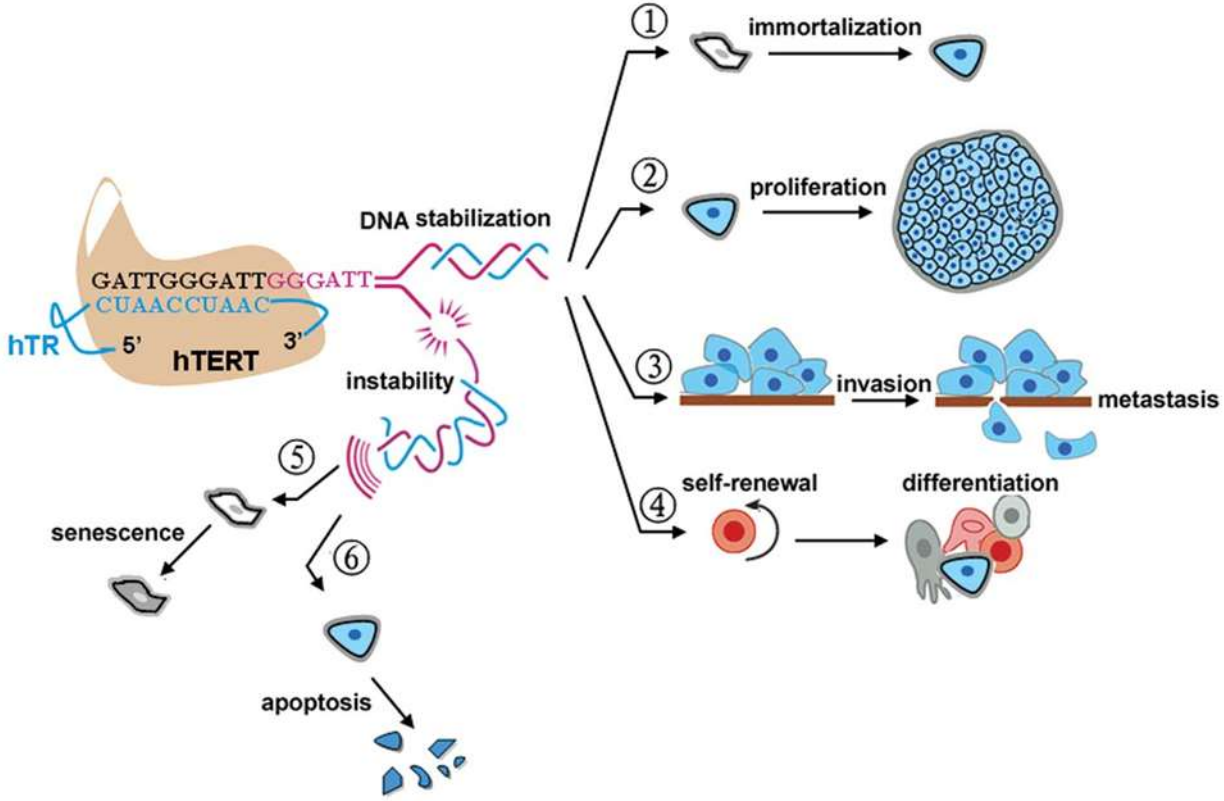


Telomers, telomerase





Polyphenols in the regulation of telomerase, hTERT



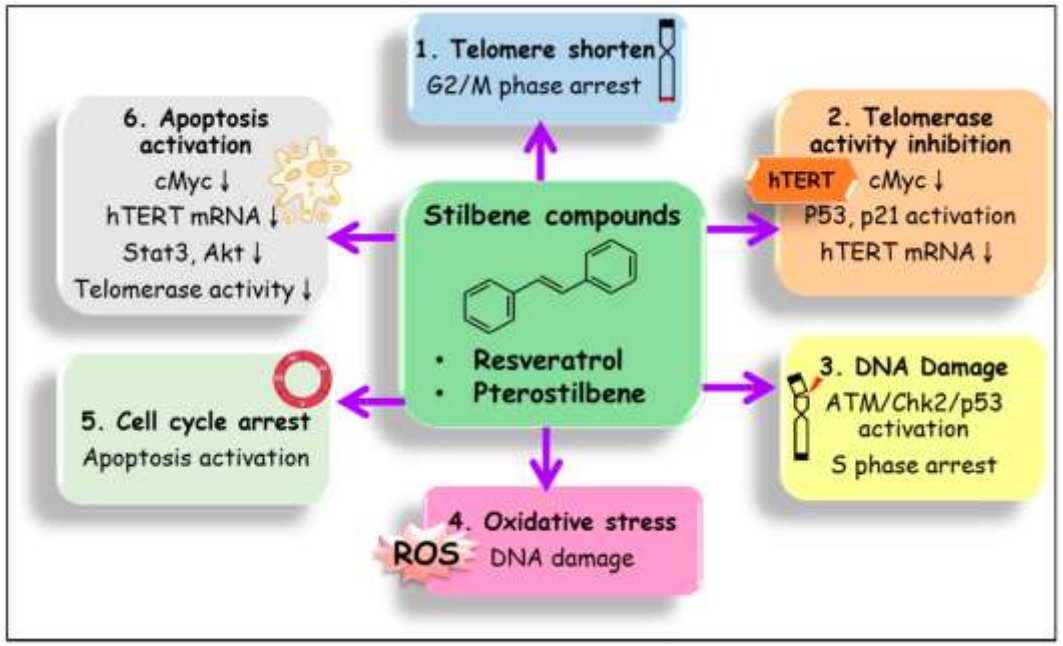


Table 1. Recent anti-aging agents as a telomerase activator, a SIRT1 activator and a senolytics

Anti-aging agents	Sources	Positive efficacy	Ref.
Cycloastragenol (TA-65)	Astragalus membranaceus	Telomeraseactivator	[5, 41]
GRN510	GRN665/TAT2	Telomerase activator	[18]
AGS-500	Synthetic triaryl compounds	Telomerase activator	[34]
Genistein	Soy bean	Telomerase activator	[4]
Centella asiatica extract	*Centella asiatica*	Telomerase activator	[36]
Maslinic acid	Olive-pomace oil	Telomerase activator	[36]
Resveratrol	Natural phenol	SIRT1 activator	[6, 20]
NAD	Coenzyne	SIRT1 activator	[16]
1,4-Dihydropyridincs	Pyridine derivatives	SIRT1 activator	[24, 38]
Ginsenosides	Natural triterpene saponins	SIRT1 activator	[33]
Melatonin	Hormon	SIRT1 activator	[14]
Navitoclax	Synthetic compound	Senolytics via Bcl2/Bcl-xL	[21]
Dasatinib+Quercetin	Synthetic compound+ Natural flavonol	Senolytics via p53/p21, tyrosinase kinase	[16]
Fisetin	Natural polyphenol	Senolytics via PI3K/Akt	[40]
17-DMAG	Synthetic compound	Senolytics via HSP90	[14]
Gal-duocamycin	Substrate of SA-β-galactosidase	Senolytics via SA-β-galactosidase	[13]
SSK1	Substrate of SA-β-galactosidase	Senolytics via SA-β-galactosidase	[13]

EGCG telomerase, cmyc, hTERT

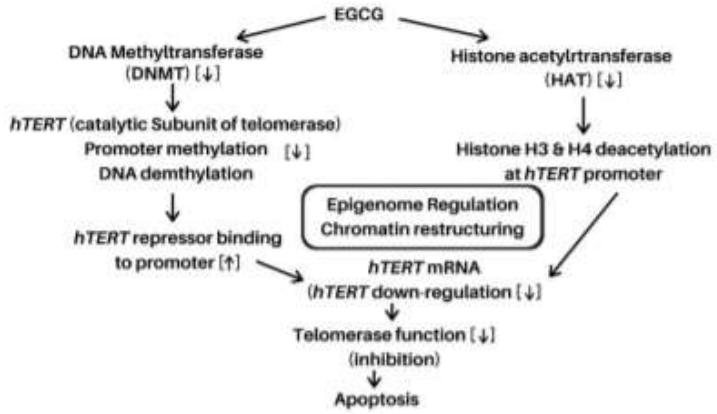
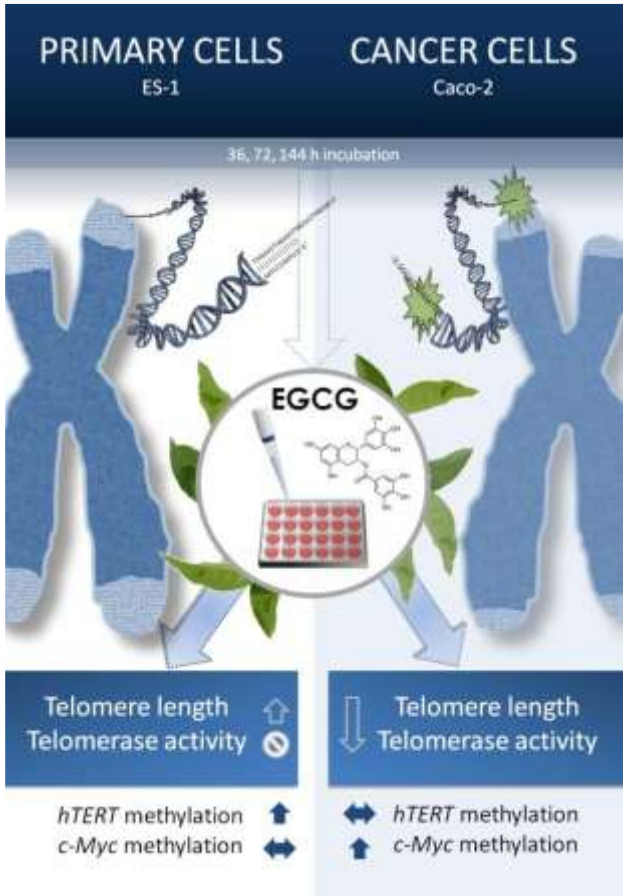


Figure 12. Mechanism of EGCG-induced apoptosis in cancer cells through epigenetic regulation of telomerase. EGCG inhibits both deoxyribonucleic acid (DNA) methyltransferase (DNMT) and histone acetyltransferase (HAT), leading to the DNA demethylation and histones H3 and H4 deacetylation of the

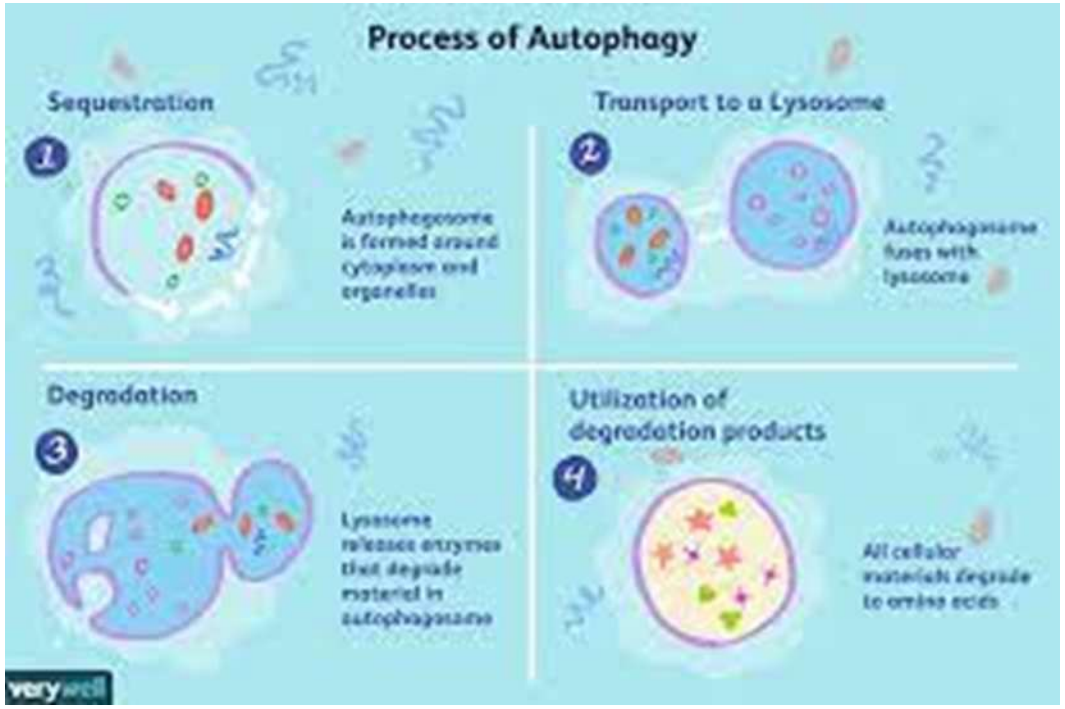
human telomerase– reverse transcriptase (hTERT) promoter, respectively. These events result in the epige-

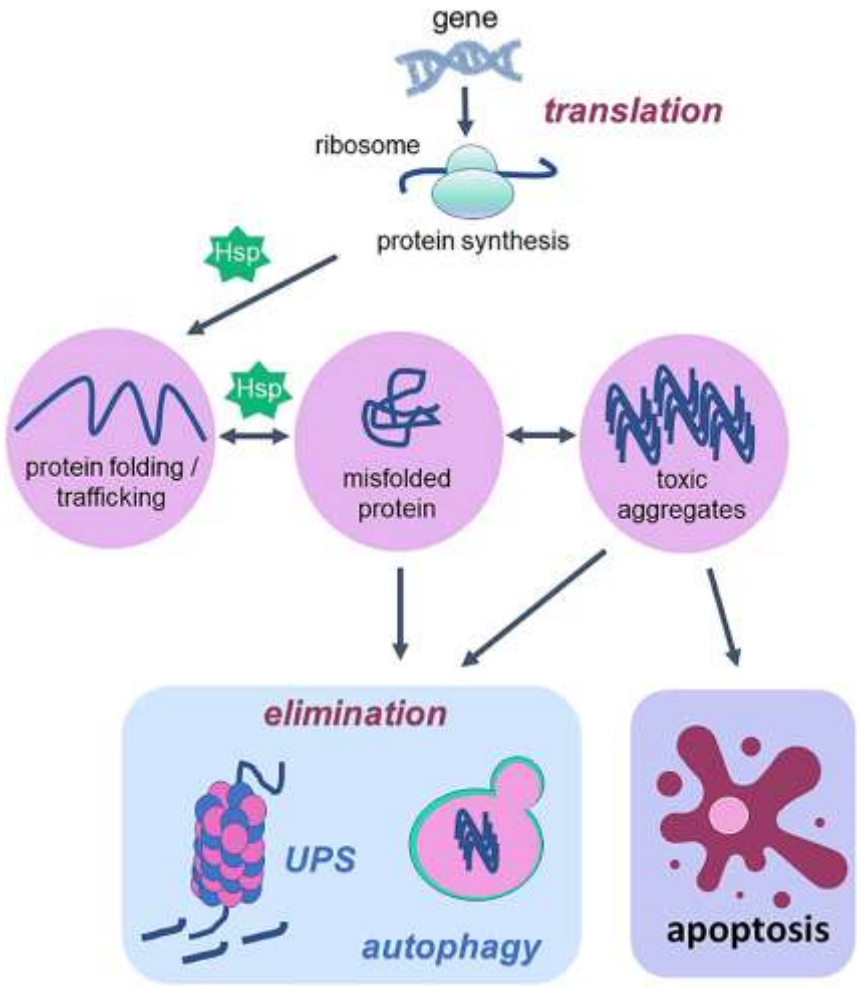


FFHD

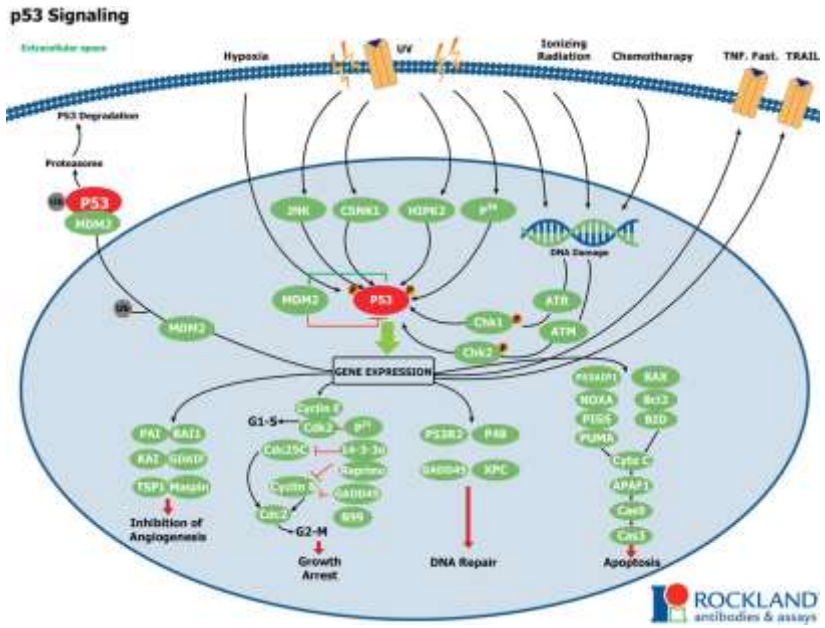
The green tea polyphenol EGCG is differentially associated with telomeric regulation in normal human fibroblasts versus cancer cells

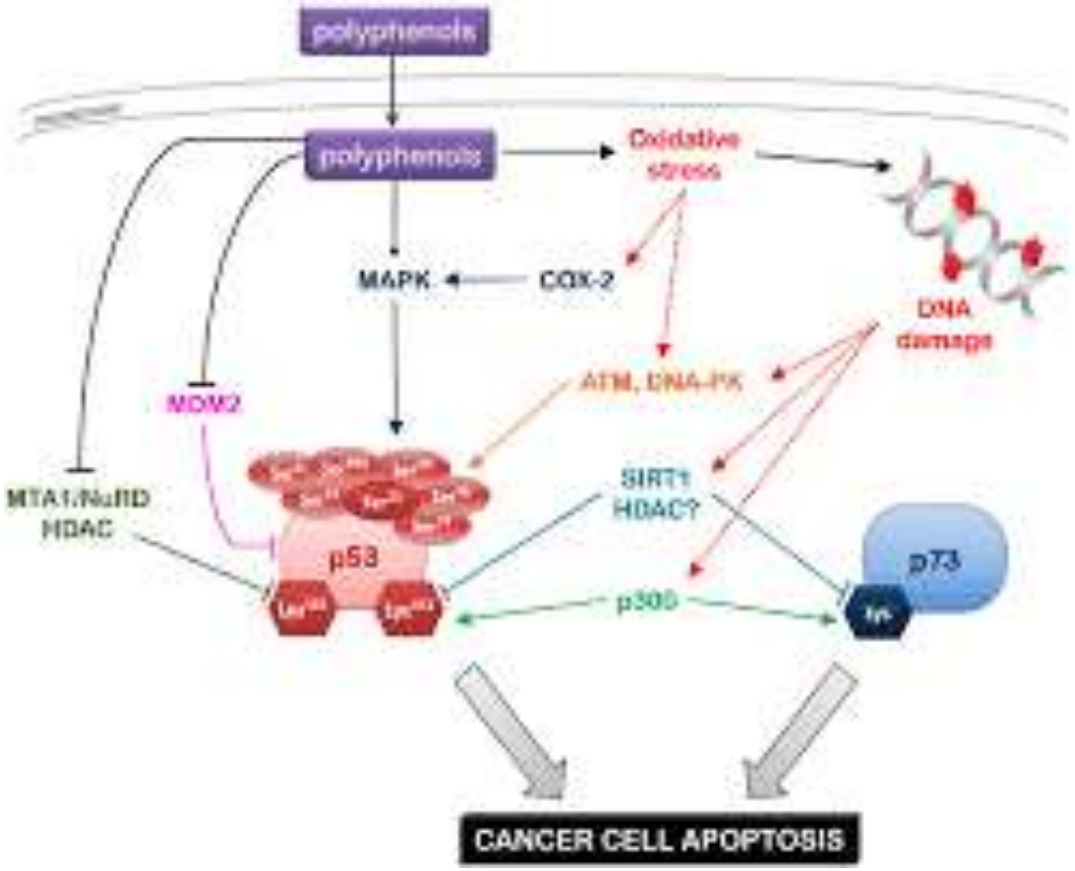
Autophagy, apoptosis





Apoptosis, p53 and polyphenols





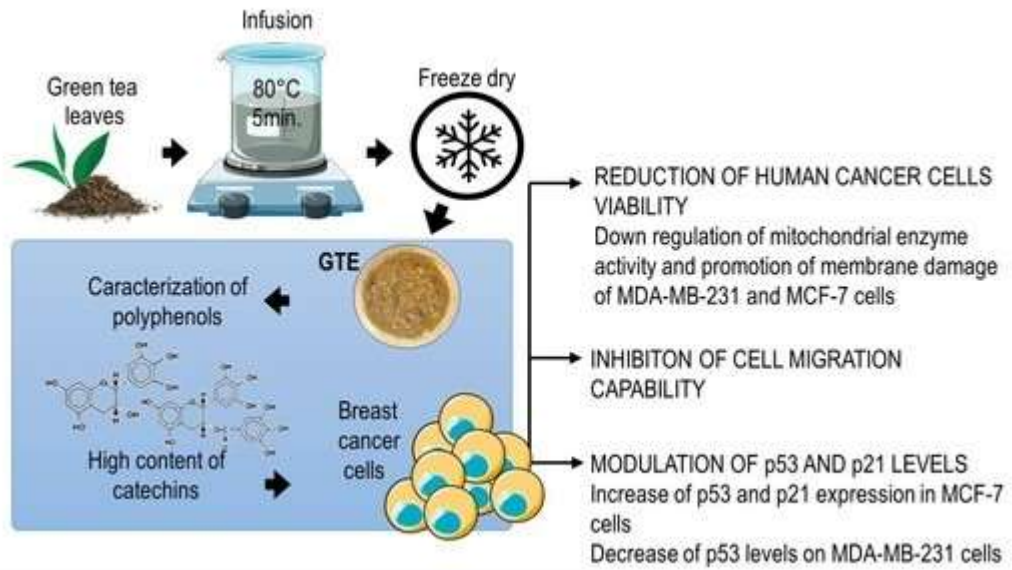
PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Green Tea Polyphenols Induce p53-Dependent and p53-Independent Apoptosis in Prostate Cancer Cells through Two Distinct Mechanisms

Karishma Gupta, Vijay S. Thakur, Natarajan Bhaskaran, Akbar Nawab, Melissa A. Babcook, Mark W. Jackson, Sanjay Gupta



Senescence and polyphenols

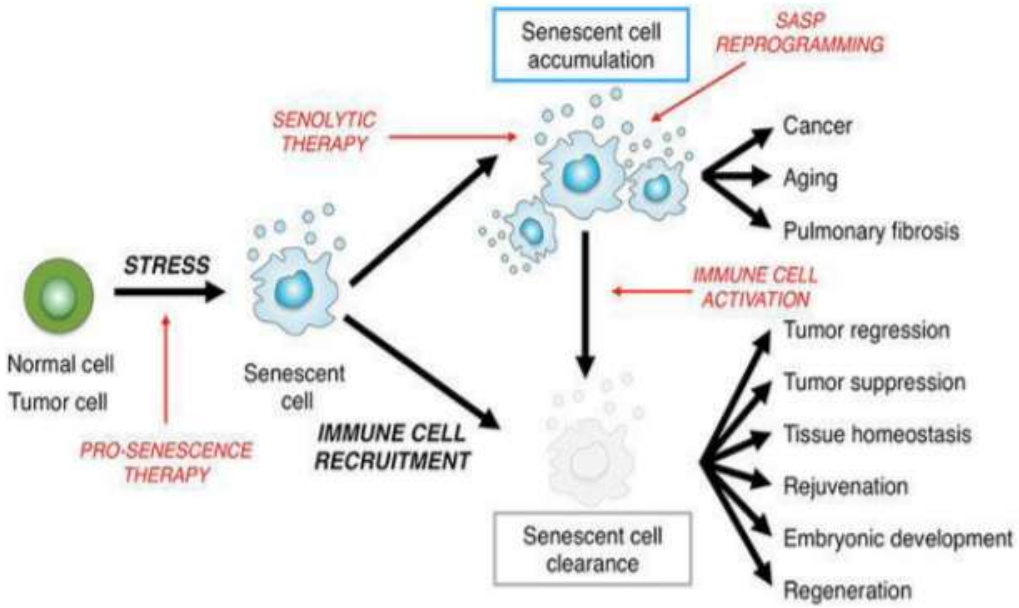
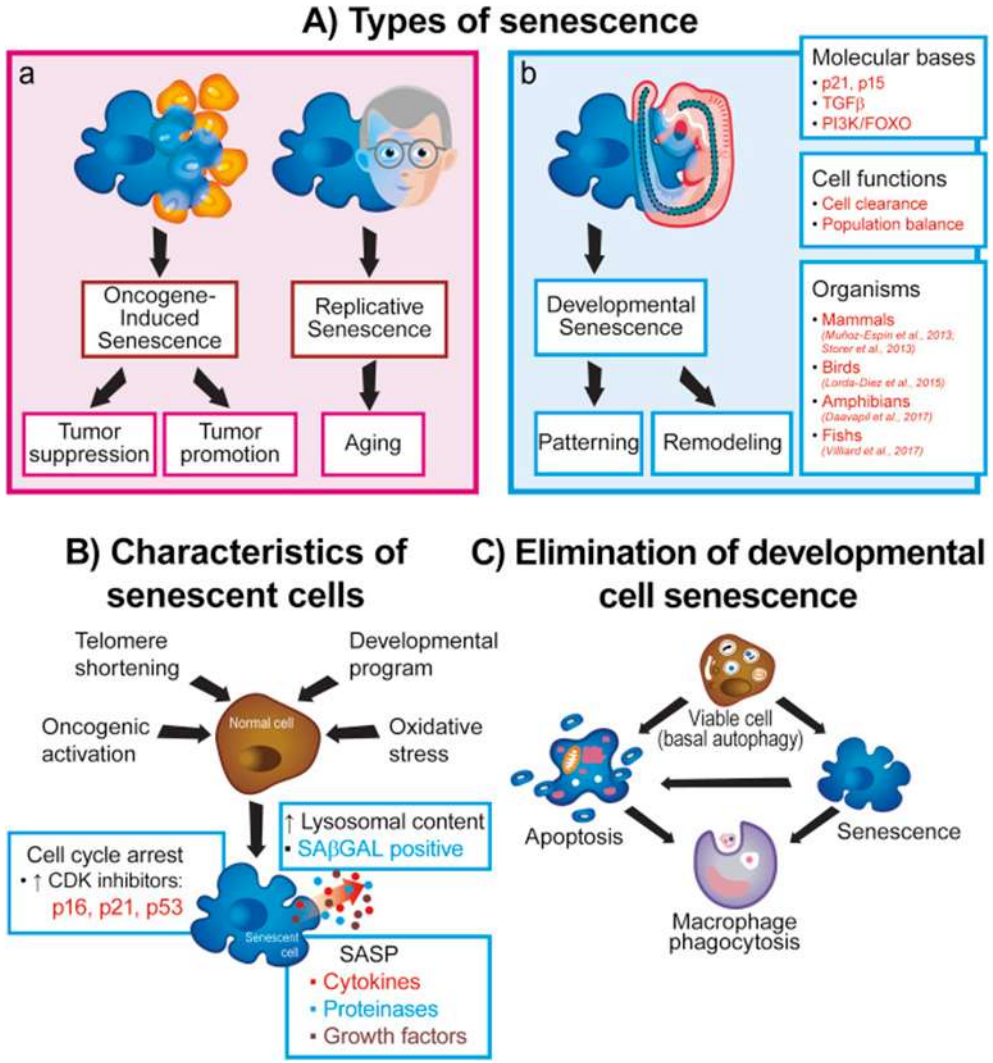


Figure 16. Clearance of senescent cells and therapeutic options. Cellular senescence is more than an anti-proliferative program. Senescent cells secrete factors that constitute the senescence-associated secretory phenotype (SASP). Cellular senescence is followed by senescent cell clearance within those processes that are considered beneficial. However, if the elimination of senescent cells does not occur, senescent cells accumulate and can lead to cancer and aging. Different therapeutic strategies (in red) can be used to exploit the beneficial aspects of cellular senescence and repress the negative ones [150].



Polyphenols and senescence

Review

Natural Polyphenols Targeting Senescence: A Novel Prevention and Therapy Strategy for Cancer

Yan Bian, Juntong Wei, Changsheng Zhao and Guorong Li *

Shandong Provincial Key Laboratory of Animal Resistant, School of Life Sciences, Shandong Normal University, Jinan 250014, Shandong, China; 2017020748@stu.sdnu.edu.cn (Y.B.); 2017020759@stu.sdnu.edu.cn (J.W.); 2017020758@stu.sdnu.edu.cn (C.Z.)

* Correspondence: grli@sdnu.edu.cn; Tel.: 86-531-86182690

Received: 3 December 2019; Accepted: 17 January 2020; Published: 20 January 2020

Abstract: Cancer is one of the most serious diseases endangering human health. In view of the side effects caused by chemotherapy and radiotherapy, it is necessary to develop low-toxic anti-cancer compounds. Polyphenols are natural compounds with anti-cancer properties and their application is a considerable choice. Pro-senescence therapy is a recently proposed anti-cancer strategy and has been shown to effectively inhibit cancer. It is of great significance to clarify the mechanisms of polyphenols on tumor suppression by inducing senescence. In this review, we delineated the characteristics of

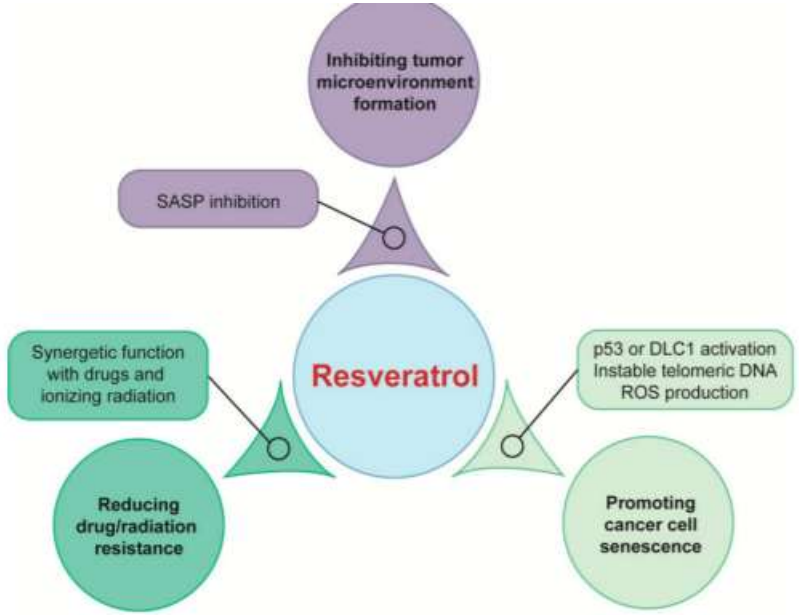
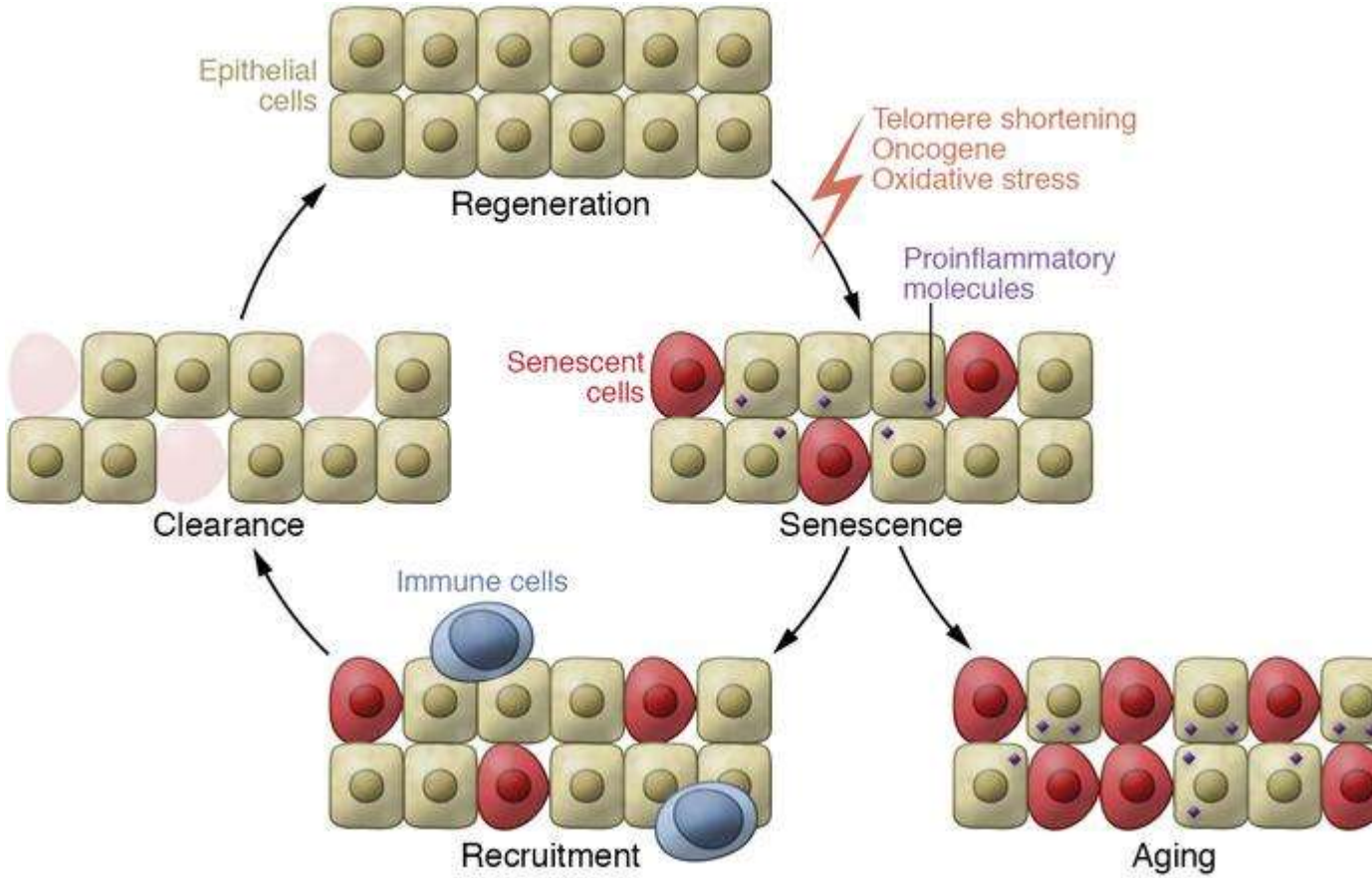


Figure 2. Potential functions of resveratrol in anti-tumor therapy. Resveratrol inhibit tumor microenvironment for cancer prevention, reduce drug/radiation resistance and induce cancer cell senescence for cancer therapy. SASP, senescence-associated secretory phenotype; DLC1, deleted in liver cancer1; ROS, reactive oxygen species.

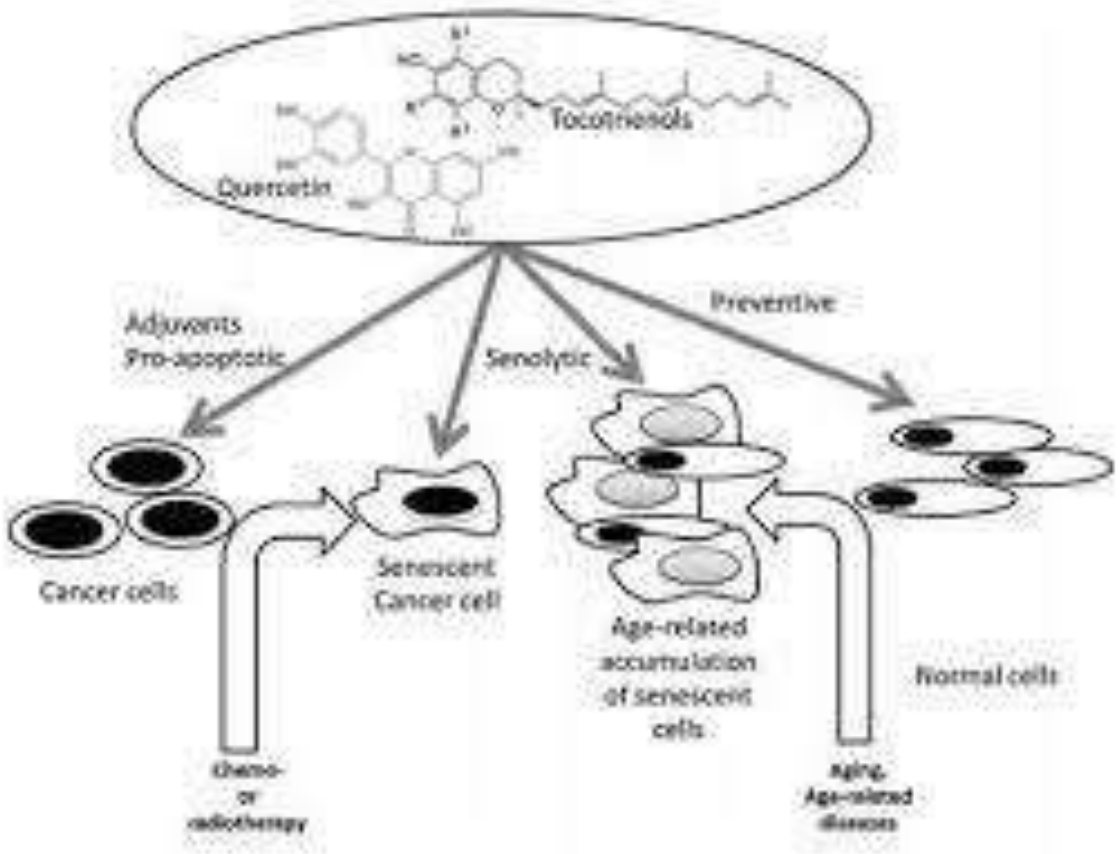
Senolytics between rejuvention of tissues and cancer prevention

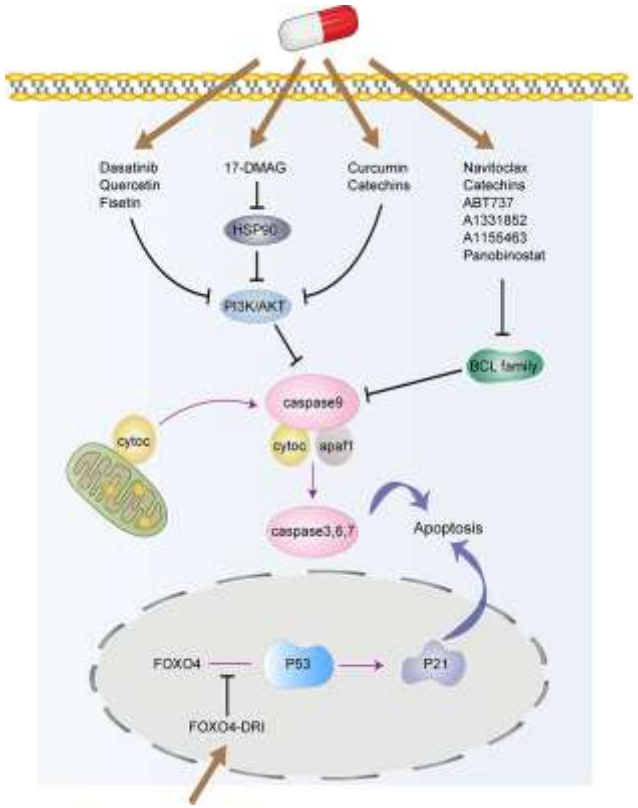
Table 1. Polyphenols and polyphenol derivatives as cancer cell senescence inducers and their effect c

Classification	Compounds	Concentration	Pathways
Resveratrol and its derivatives	Resveratrol	25/50 (μM)	p53/CXCR2
		50 (μM)	BRCA1/DDR
		30 (μM)	ROS/DDR
		100 (μM)	ROS/DLC1/SASP
		6/20 (μM) 100 (μM)	Histone H2B Pokemon
		25/50 (μM)	SIRT1
		50 (μM)	Rictor/RhoA-GTPase
	Pterostilbene	2.5/5/50 (μM)	hTERT/DDR
	Pauciflorol B	10 (μM)	p16/Rb
	3,3′,4,4′-tetrahydroxy-trans-stilbene	10/50/100 (μM)	ROS DDR
Flavonoids	Quercetin	50/100/200 (μM)	RAS/MAPK/ERK PI3K/AKT
	Beta-naphthoflavone	10 (μM)	PI3K/AKT/cyclinD1/D3 MAPK/ERK
	Baicalin	10/20/40 (μM)	DEPP/RAS/Raf/MEK/ERK DEPP/p16/Rb
	IdB 1016	63.2/126.5 (μg/mL)	HER-2/neu p53
	Diosmin	5/10 (μM)	ROS DDR
	Apigenin	Above 25 (μM)	ROS/RNS p16/cyclin D1/p-Rb p21/cyclin E/p-Rb
	Coumestrol	50 (μM)	CKII/ROS/p53/p21
	Rotenone	0.4 (μM)	Ca^{2+}/ROS
	Epigallocatechin gallate	10 (μM)	DDR
	Oroxin A	5/10/15/20 (μM)	p38/ER stress
	Cristacarpin	1 (μM)	p38/ER stress/ROS/p21
	Flavokawain B	3 (μg/mL)	ATF4/DDIT3/TRIB3/AkT/mTOR

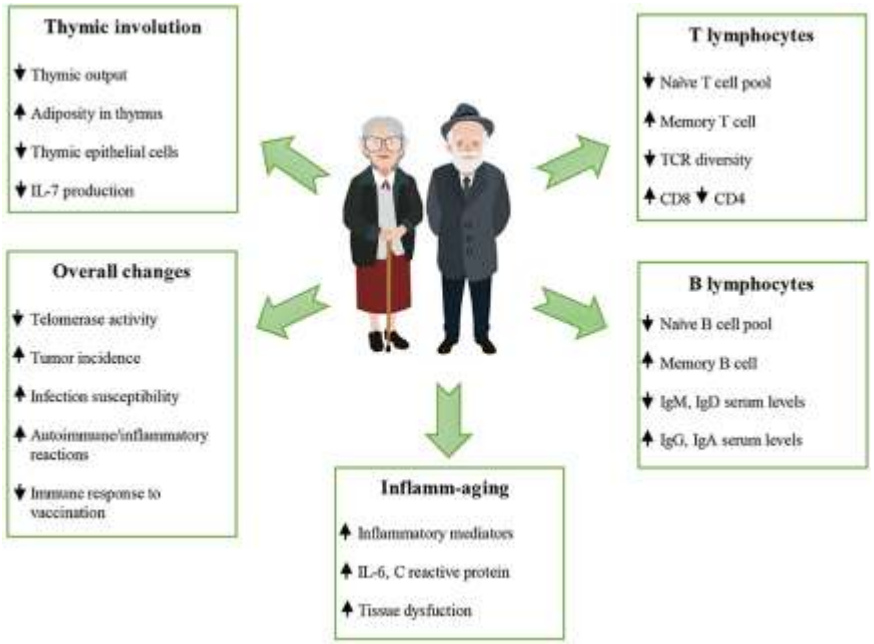


Quecetin, senolytics and markets millio $ markets





Immuno senescence and nutraceuticals



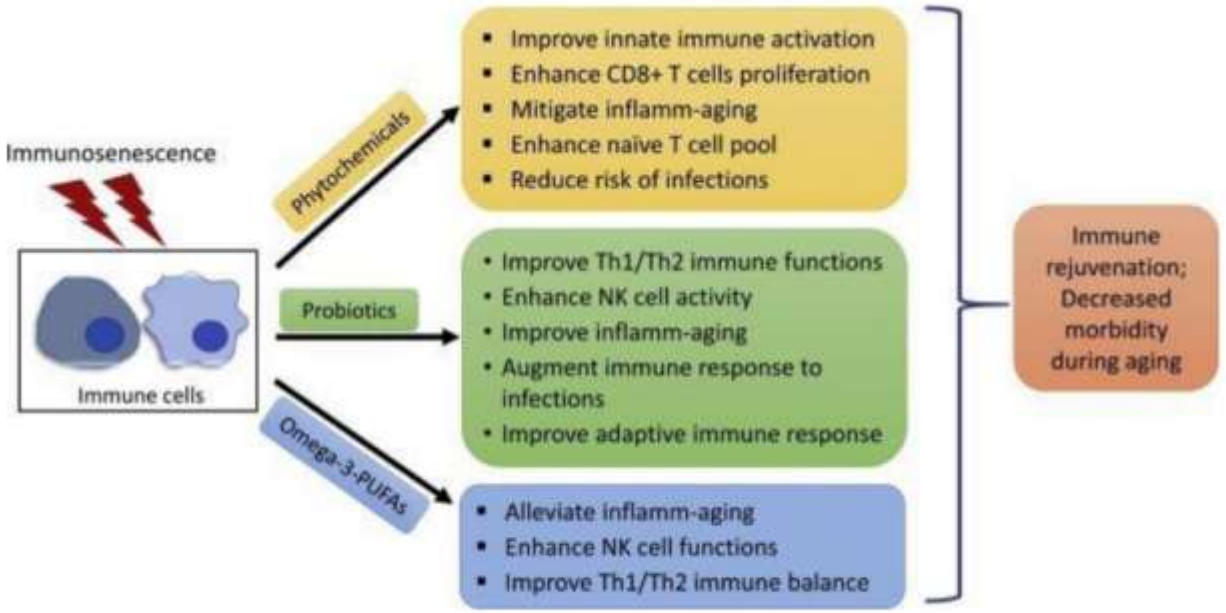
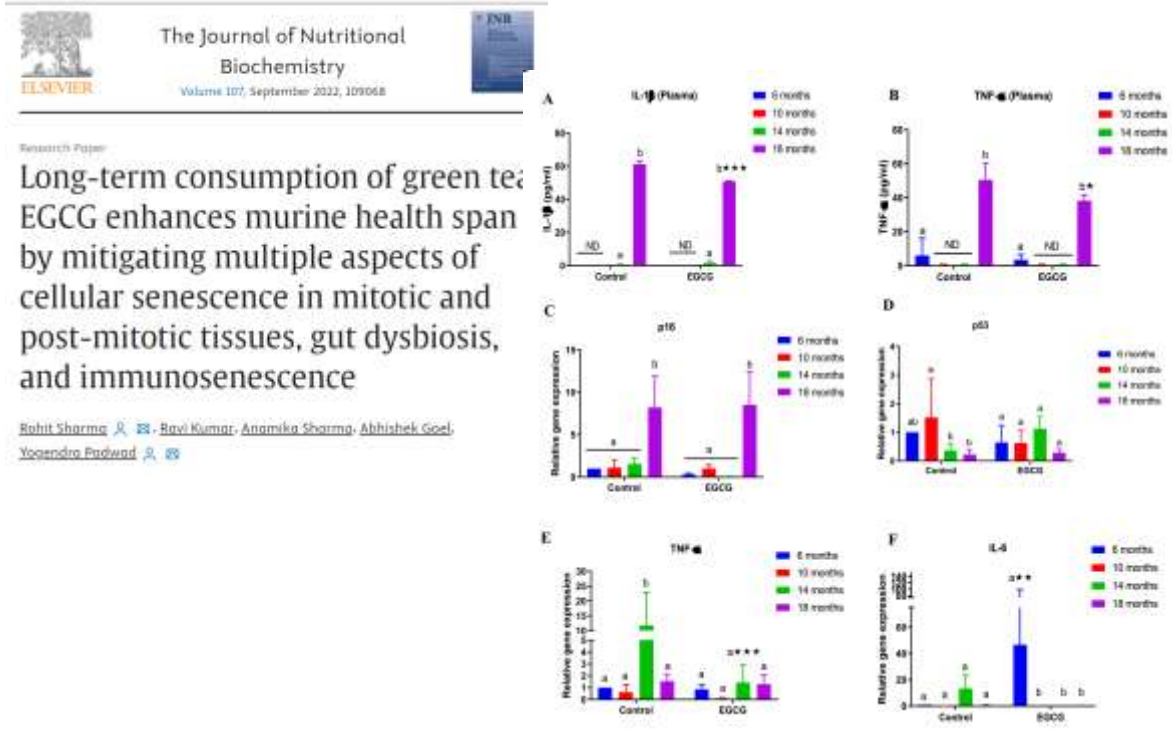
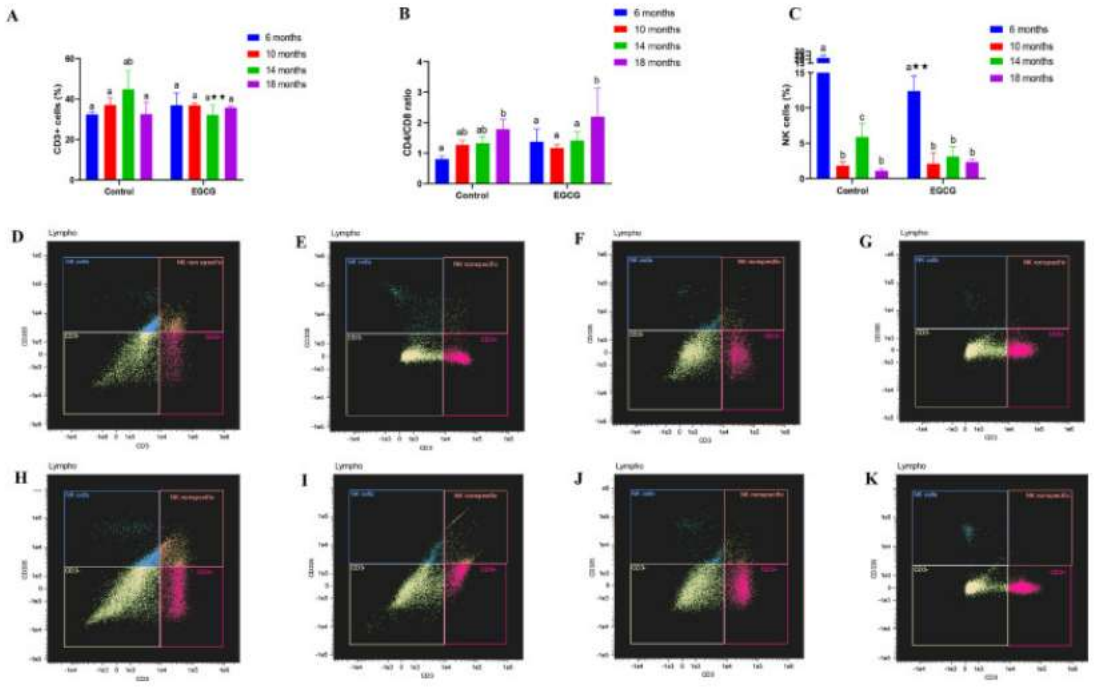


Figure 13. Nutraceuticals-Based Immunotherapeutic Concepts and Opportunities for the Mitigation of Cellular Senescence and Aging



Effect of EGCG consumption on innate immune functions. Animals were divided into four control groups and four EGCG fed groups, and one group each from control and EGCG groups was sacrificed after every 4 months of feeding till 18 months of animal age. Plasma levels of (A) IL-1β (B) TNF-α.

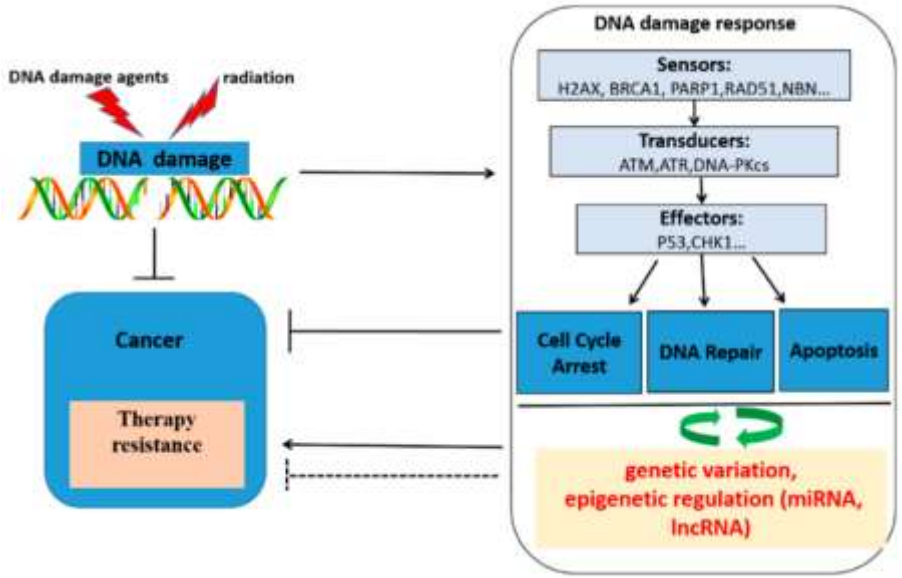


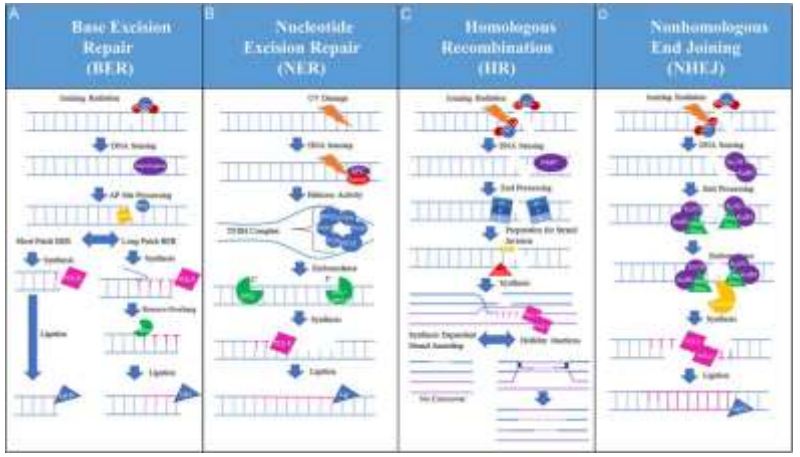
Download : Download high-res image (999KB)

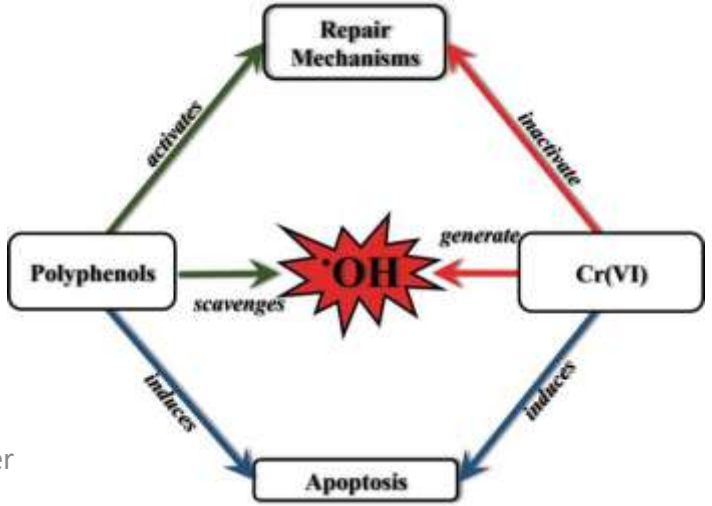
Download : Download full-size image

Fig. 7. Effect of EGCG consumption on splenic T cell proliferation and activation. Animals were divided into four control groups and four EGCG fed groups, and one group each from control and EGCG groups was sacrificed after every 4 months of feeding till 18 months of animal age. Abundance of **(A)** CD3+ cells **(B)** CD4/CD8 ratio **(C)** NK cells.

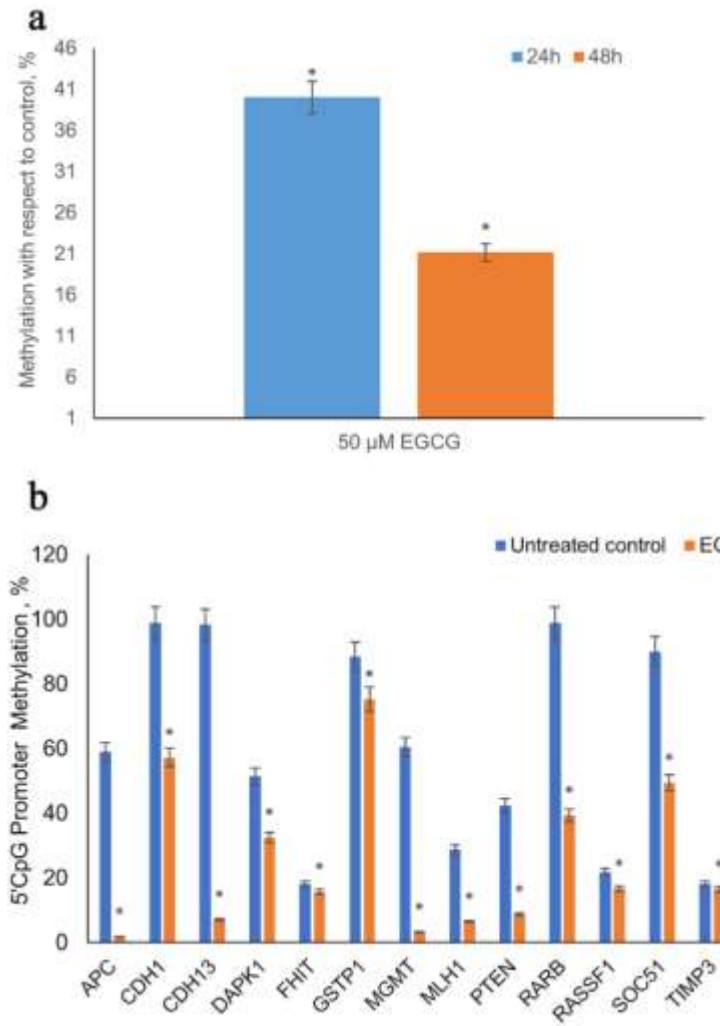
Aging DNA-damage response, DNA-repair, Epigenetics, Polyphenols

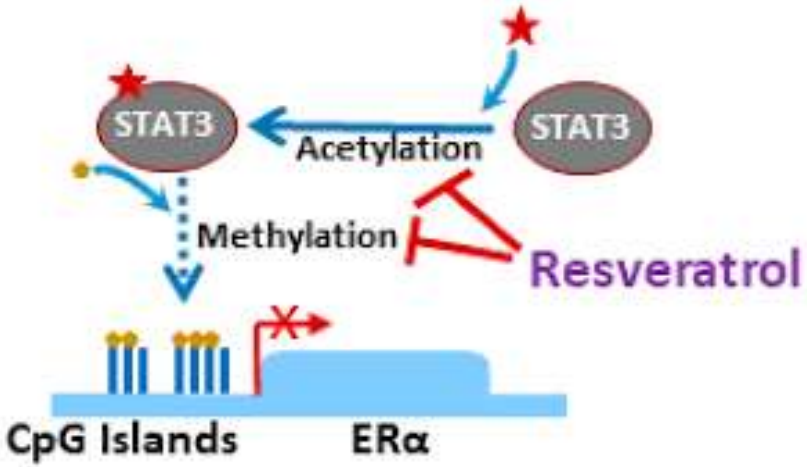




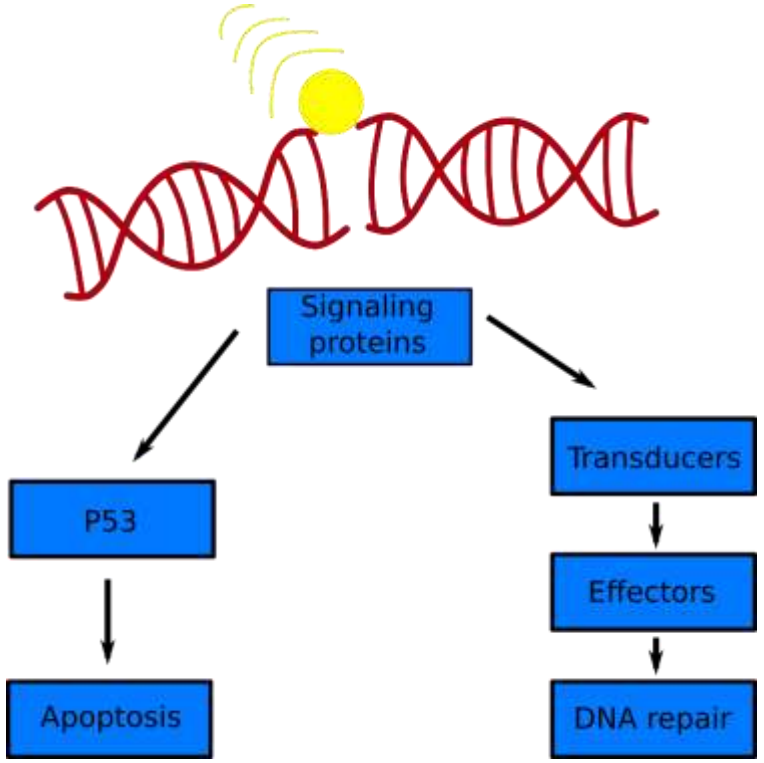


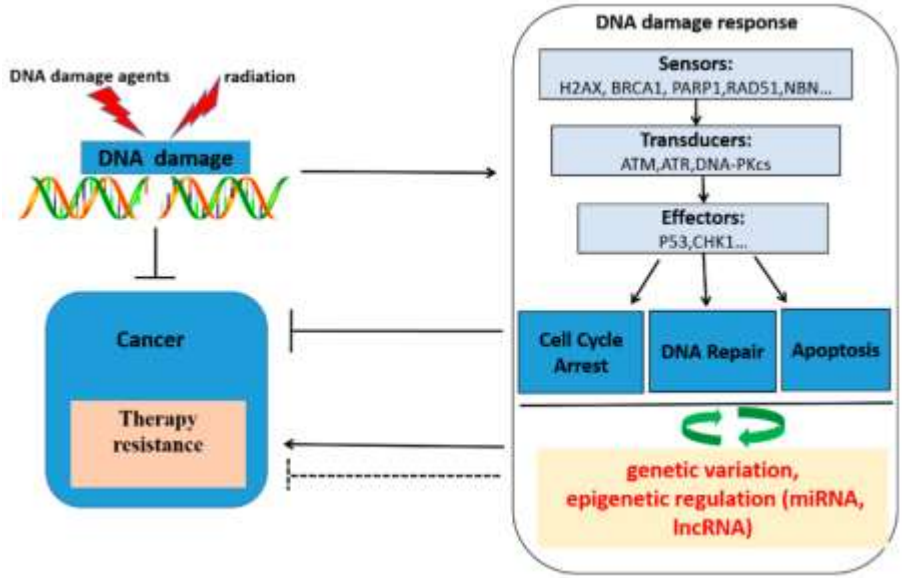
MGMT and MLH1 DNA repair enymes and promotor methylation, EGCG





Epigenetics regulates DNA repair





Mouse study: EGCG reduced high fat diet induced strandbreaks, DNmt1, comet assay

Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2017, Article ID 3079148, 17 pages
https://doi.org/10.1155/2017/3079148

Hindawi

Research Article

EGCG Prevents High Fat Diet-Induced Changes in Gut Microbiota, Decreases of DNA Strand Breaks, and Changes in Expression and DNA Methylation of *Dnmt1* and *MLH1* in C57BL/6J Male Mice

Marlene Remely,[1] Franziska Ferk,[2] Sonja Sterneder,[1] Tahereh Setayesh,[2] Sylvia Roth,[1] Tatjana Kepcija,[1] Rahil Noorizadeh,[2] Irene Rebhan,[1] Martina Greunz,[1] Johanna Beckmann,[1] Karl-Heinz Wagner,[1] Siegfried Knasmüller,[2] and Alexander G. Haslberger[1]

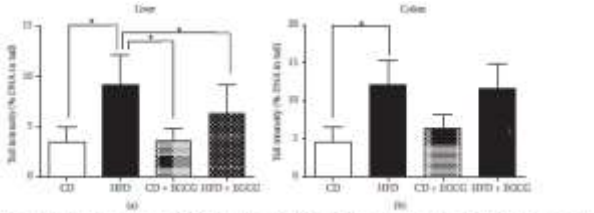
European Journal of Nutrition
https://doi.org/10.1007/s00394-018-1782-2

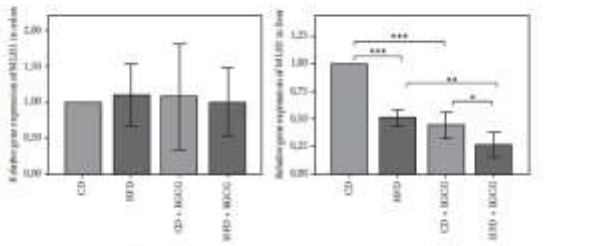
ORIGINAL CONTRIBUTION

CrossMark

Gallic acid, a common dietary phenolic protects against high fat diet induced DNA damage

Tahereh Setayesh[1] · Armen Nersesyan[1] · Miroslav Mišík[1] · Rahil Noorizadeh[1,3] · Elisabeth Haslinger[1] · Tahereh Javaheri[2,3] · Elisabeth Lang[1] · Michael Grusch[1] · Wolfgang Huber[1] · Alexander Haslberger[4] · Siegfried Knasmüller[1]





Aging, ageotypes and prevention

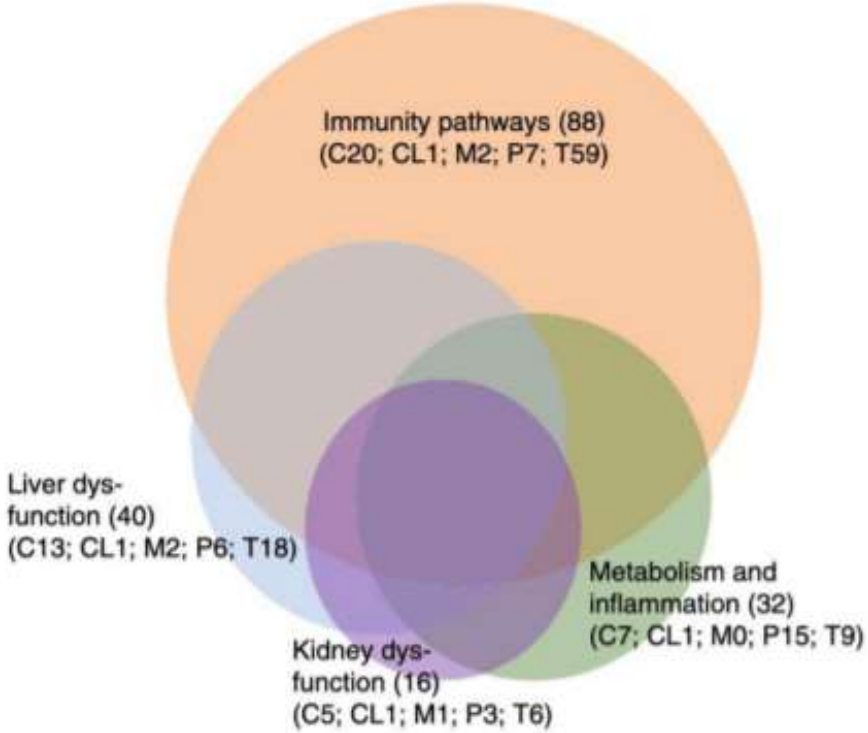
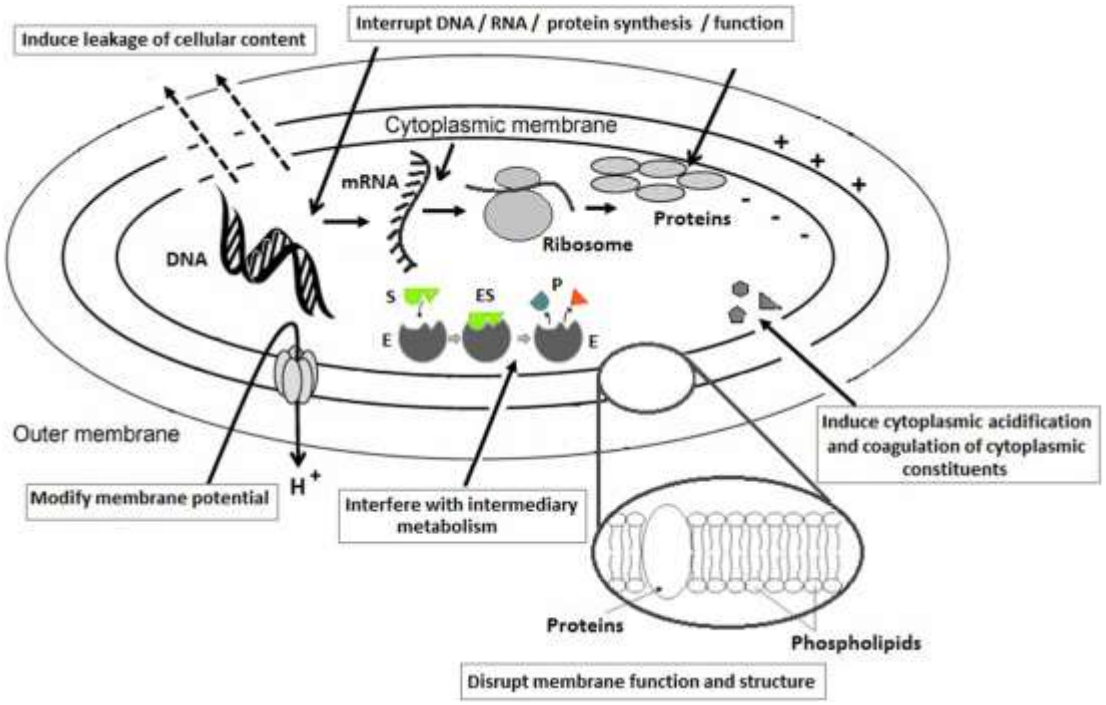
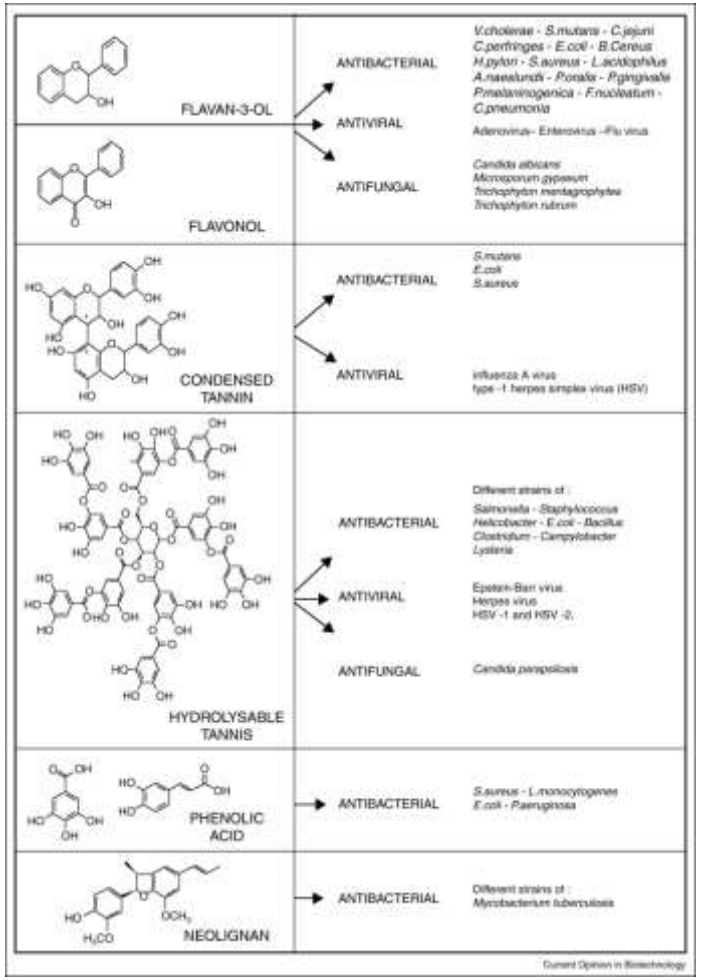


Figure 21. Ageotypes, personalized aging [186]

Anti bacterial polyphenols





Antiviral nutraceuticals

Fermented products
Probiotics enhance gut bacteria & gut–lung axis-related respiratory fitness

Herbs & roots
Prevent viral replication, enhance anti-influenza virus IgG and IgA antibodies production & T-cell function

Dairy products
Vitamin D lowers viral replication, reduce infection rate & lung pneumonia

Fish, chicken & meat
Immune defence; peptides enhance monocytes & macrophages functions & prevent infected lung injury

Antiviral Functional Foods

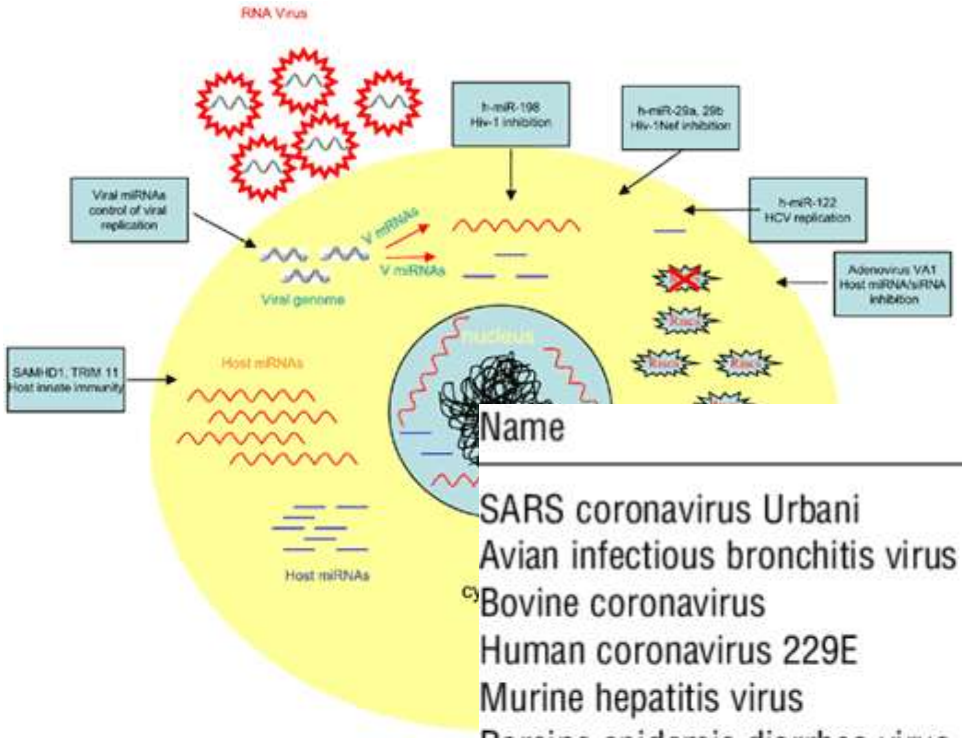
Fruit and vegetables
Vitamins & minerals antioxidant immune protection of respiratory system. Plant cyclotides prevent T-cells malfunction

Coffee
Decreases progeny virus yield, neutrophil & monocyte chemotaxis, lipopolysaccharide & prevent mucosal response to influenza pathogens

Nuts & seeds
Immuno-protective phenolic compounds for high-risk groups

Olive Oil
Prevents respiratory syncytial virus & influenza A, B, parainfluenza 1, 2 & 3 viruses

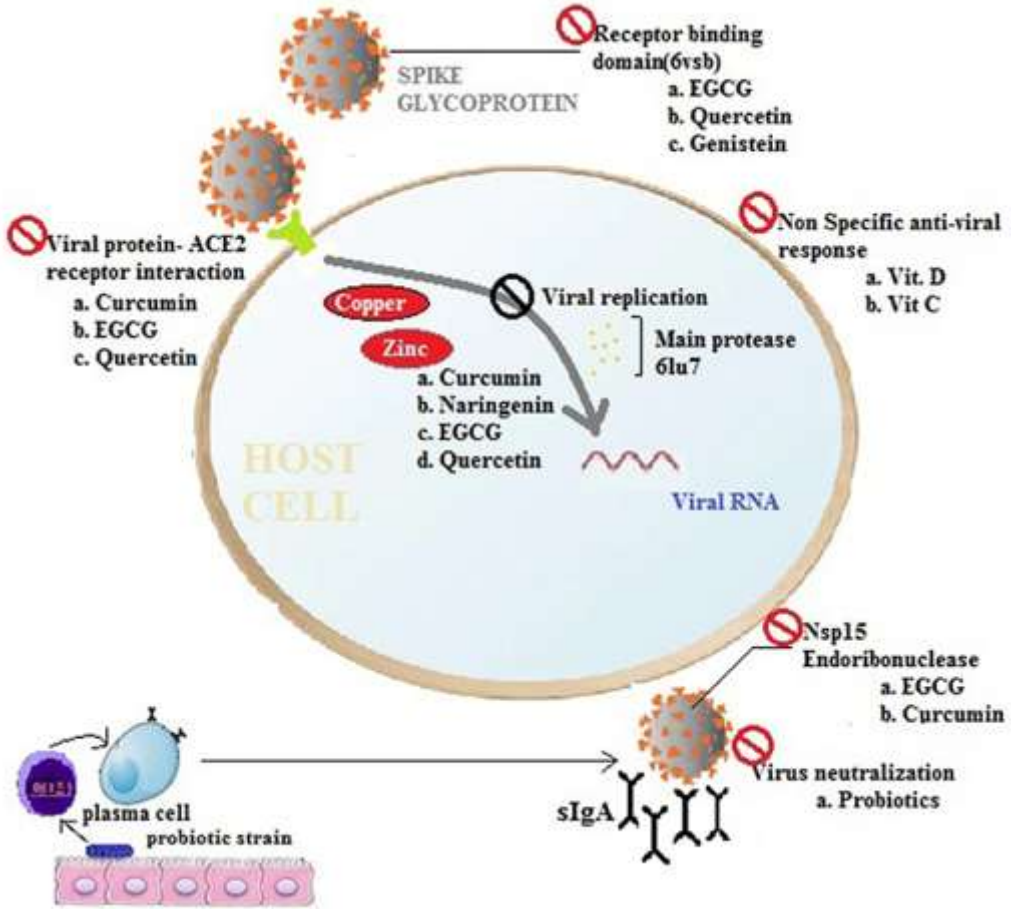
RNA and Corona viruses

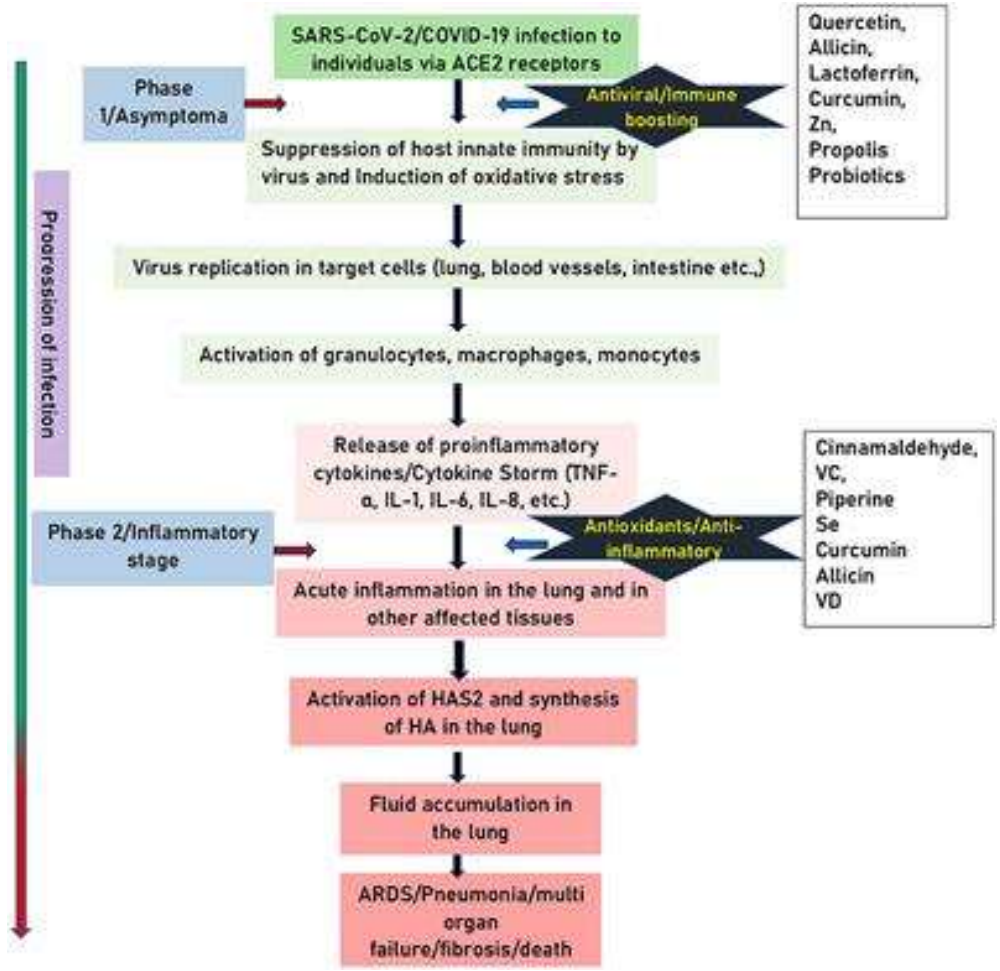


Name	Abbrev.	Accession	Length	Base composition
SARS coronavirus Urbani	SARS	AY278741	29,727	(0.28, 0.20, 0.21, 0.31)
Avian infectious bronchitis virus	AIBV	NC_001451.1	27,608	(0.29, 0.16, 0.22, 0.33)
Bovine coronavirus	BCoV	NC_003045.1	31,028	(0.27, 0.15, 0.22, 0.36)
Human coronavirus 229E	HCoV	NC_002645.1	27,317	(0.27, 0.17, 0.22, 0.35)
Murine hepatitis virus	MHV	NC_001846	31,357	(0.26, 0.18, 0.24, 0.32)
Porcine epidemic diarrhea virus	PEDV	NC_003436.1	28,033	(0.25, 0.19, 0.23, 0.33)
Transmissible gastroenteritis virus	TGV	NC_002306.2	28,586	(0.29, 0.17, 0.21, 0.33)
Rubella virus	RUV	NC_001545.1	9,755	(0.15, 0.39, 0.31, 0.15)
Equine arteritis virus	EAV	NC_002532.2	12,704	(0.21, 0.26, 0.26, 0.27)
Rabies virus	RV	NC_001542.1	11,932	(0.29, 0.22, 0.23, 0.26)
Human immunodeficiency virus 1	HIV-1	NC_001802.1	9,181	(0.36, 0.18, 0.24, 0.22)

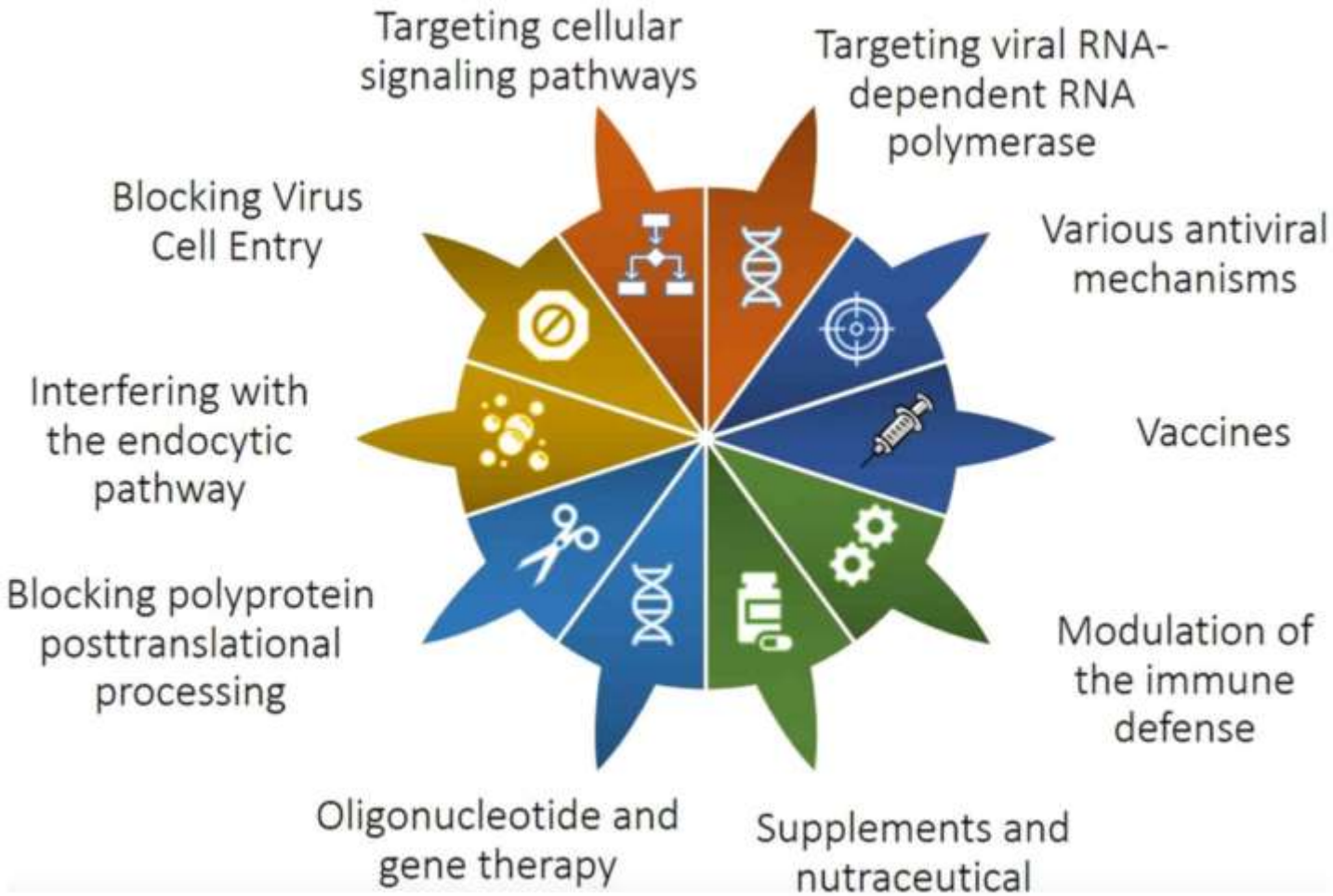
S. No.	Molecule	Target	Type of Study/ Techniques Used	Results	Study, Year, Reference
1	Luteolin	SARS-CoV S2 protein	• Frontal-affinity chromatography-mass spectrometry • HIV-luc/SARS pseudotype virus assay • MTT assay with wild-type SARS-CoV	• Luteolin-inhibited SARS-CoV infection in a dose-dependent manner. • EC_{50} was 10.6 μM. CC_{50} was 0.155 mM. LD_{50} in mice was 232.2 mg/kg	Yi et al, 2004[11]
2	Quercetin	SARS-CoV S2 protein	HIV-luc/SARS pseudotype virus assay	EC_{50} of 83.4 μM and CC_{50} of 3.32 mM	Yi et al, 2004[11]
3	GCG (gallocatechin gallate)	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 91% inhibition by 200 μM. • IC_{50} of 47 μM. • Binding energy of −14 kcal/mol	Nguyen et al, 2012[14]
4	Quercetin	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 80% inhibition at 200 μM. • IC_{50} of 23.8 μM • Binding energy −10.2 kcal/mol	Nguyen et al, 2012[14]
5	EGCG	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 85% inhibition at 200 μM. • IC_{50} of 73 μM • Binding energy −11.7 kcal/mol	Nguyen et al, 2012[14]
6	Resveratrol	MERS-CoV NP	• MTT assay using vero-E6 cell line • Nucleocapsid protein staining	• Found to be effective in the 125–250 μM range on viral titre as well as viral RNA amount. • Inhibits caspase 3 cleavage.	Lin et al, 2017[12]
7	Hesperetin	SARS-CoV 3CLPro	Cell free and cell-based cleavage assays	IC_{50} of 60 μM in cell free assay, IC_{50} of 8.3 μM in cell-based assay and a CC_{50} of 2718 μM	Lin et al, 2005[15]
8	Quercetin	*ACE2* and *FURIN*	• Gene silencing • Expression studies • Transgenic mouse models	• Quercetin affected *ACE2* expression. • In addition, it was found to alter the expression of 98 of 332 (30%) genes encoding human proteins that serve as target for the SARS-CoV-2.	Glinsky, 2020[16]

Covid , SARS-2

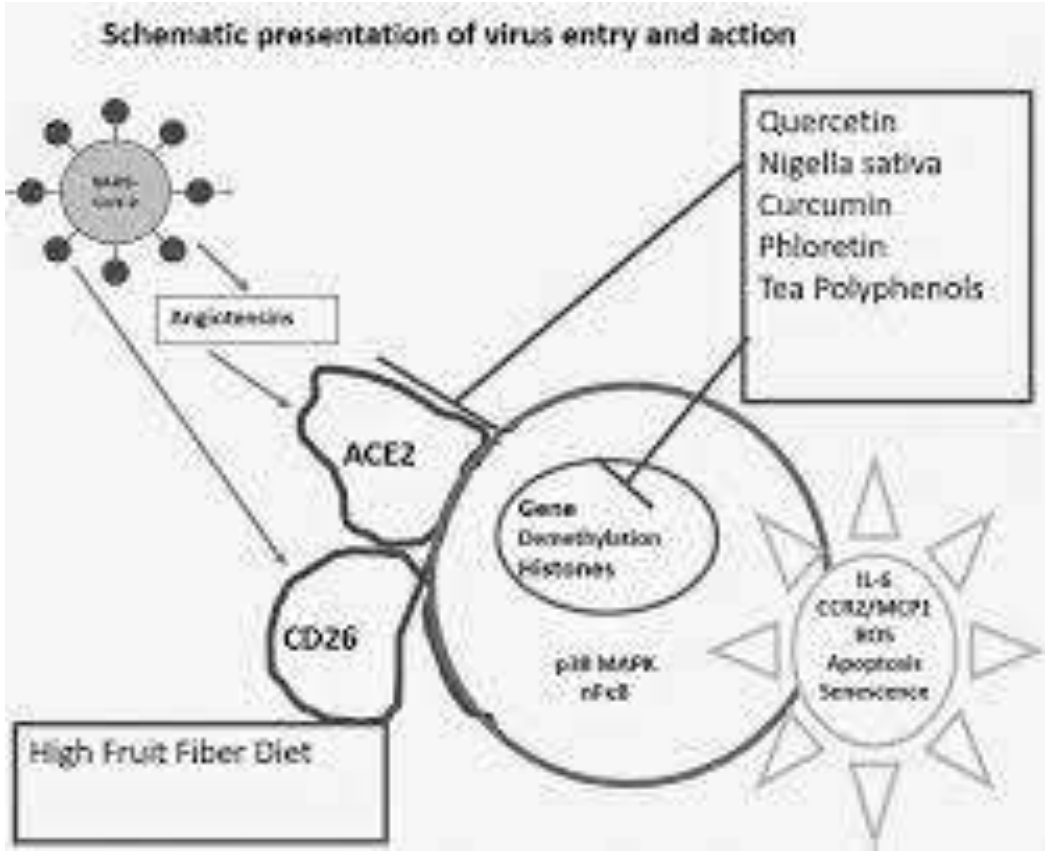

SPIKE GLYCOPROTEIN
Receptor binding domain(6vsb)
a. EGCG
b. Quercetin
c. Genistein
Viral protein- ACE2 receptor interaction
a. Curcumin
b. EGCG
c. Quercetin
Copper
Zinc
Viral replication
Main protease 6lu7
a. Curcumin
b. Naringenin
c. EGCG
d. Quercetin
Non Specific anti-viral response
a. Vit. D
b. Vit C
HOST CELL
Viral RNA
Nsp15 Endoribonuclease
a. EGCG
b. Curcumin
Virus neutralization
a. Probiotics
sIgA
plasma cell
probiotic strain

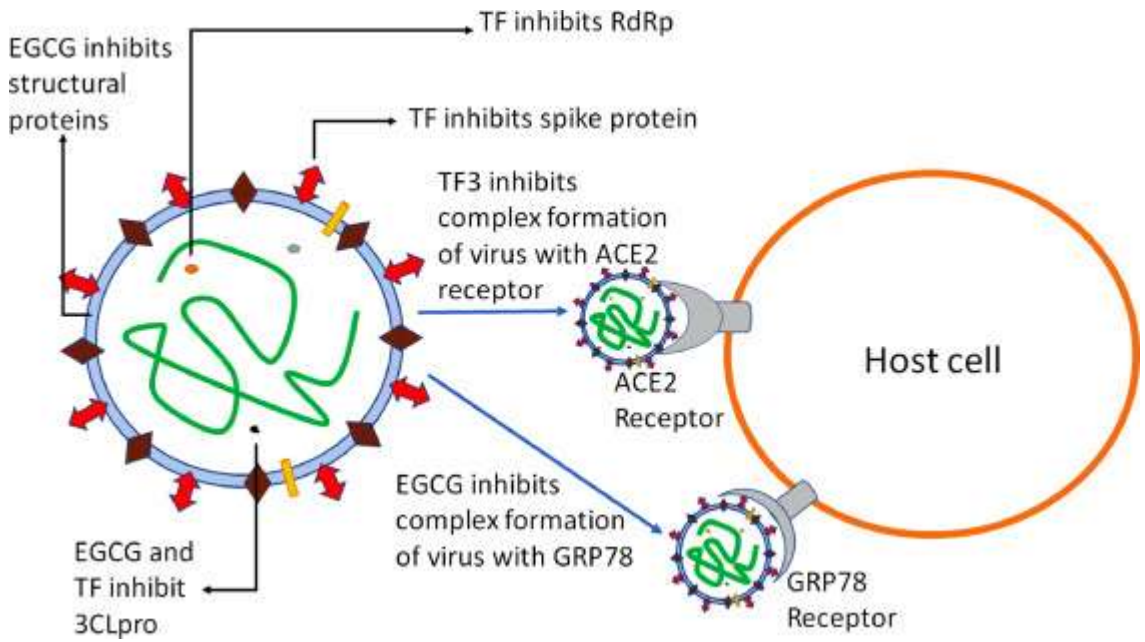

SARS-CoV-2/COVID-19 infection to individuals via ACE2 receptors
Phase 1/Asymptoma
Antiviral/Immune boosting
Quercetin, Allicin, Lactoferrin, Curcumin, Zn, Propolis Probiotics
Suppression of host innate immunity by virus and induction of oxidative stress
Progression of infection
Virus replication in target cells (lung, blood vessels, intestine etc.,)
Activation of granulocytes, macrophages, monocytes
Release of proinflammatory cytokines/Cytokine Storm (TNF-α, IL-1, IL-6, IL-8, etc.)
Phase 2/Inflammatory stage
Antioxidants/Anti-inflammatory
Cinnamaldehyde, VC, Piperine Se Curcumin Allicin VD
Acute inflammation in the lung and in other affected tissues
Activation of HAS2 and synthesis of HA in the lung
Fluid accumulation in the lung
ARDS/Pneumonia/multi organ failure/fibrosis/death

Strategies


Targeting cellular signaling pathways
Targeting viral RNA-dependent RNA polymerase
Blocking Virus Cell Entry
Various antiviral mechanisms
Interfering with the endocytic pathway
Vaccines
Blocking polyprotein posttranslational processing
Modulation of the immune defense
Oligonucleotide and gene therapy
Supplements and nutraceutical

Nutraceuticals, epigenetics and inhibition of RNA viruses





Conclusions

In conclusion fasting and to some extend fasting mimetics result in beneficial modulation of microbiota (e.g diversity, SCFA, BHP) and metabolism (e.g SIRTS, mtDNA, telomer length)

Microbiota structure seems to interfere with the expression of Sirtuins and metabolism relevant miRNAs

The EFSA ANS Panel was asked to provide a scientific opinion on the safety of green tea catechins from dietary sources including preparations such as food supplements and infusions. Green tea is produced from the leaves of Camellia sinensis (L.) Kuntze, without fermentation, which prevents the oxidation of polyphenolic components. Most of the polyphenols in green tea are catechins. The Panel considered the possible association between the consumption of (-)-epigallocatechin-3-gallate (EGCG), the most relevant catechin in green tea, and hepatotoxicity. This scientific opinion is based on published scientific literature, including interventional studies, monographs and reports by national and international authorities and data received following a public 'Call for data'. The mean daily intake of EGCG resulting from the consumption of green tea infusions ranges from 90 to 300 mg/day while exposure by high-level consumers is estimated to be up to 866 mg EGCG/day, in the adult population in the EU. Food supplements containing green tea catechins provide a daily dose of EGCG in the range of 5–1,000 mg/day, for adult population. The Panel concluded that catechins from green tea infusion, prepared in a traditional way, and reconstituted drinks with an equivalent composition to traditional green tea infusions, are in general considered to be safe according to the presumption of safety approach provided the intake corresponds to reported intakes in European Member States. However, rare cases of liver injury have been reported after consumption of green tea infusions, most probably due to an idiosyncratic reaction. Based on the available data on the potential adverse effects of green tea catechins on the liver, the Panel concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG/day taken as a food supplement has been shown to induce a statistically significant increase of serum transaminases in treated subjects compared to control.

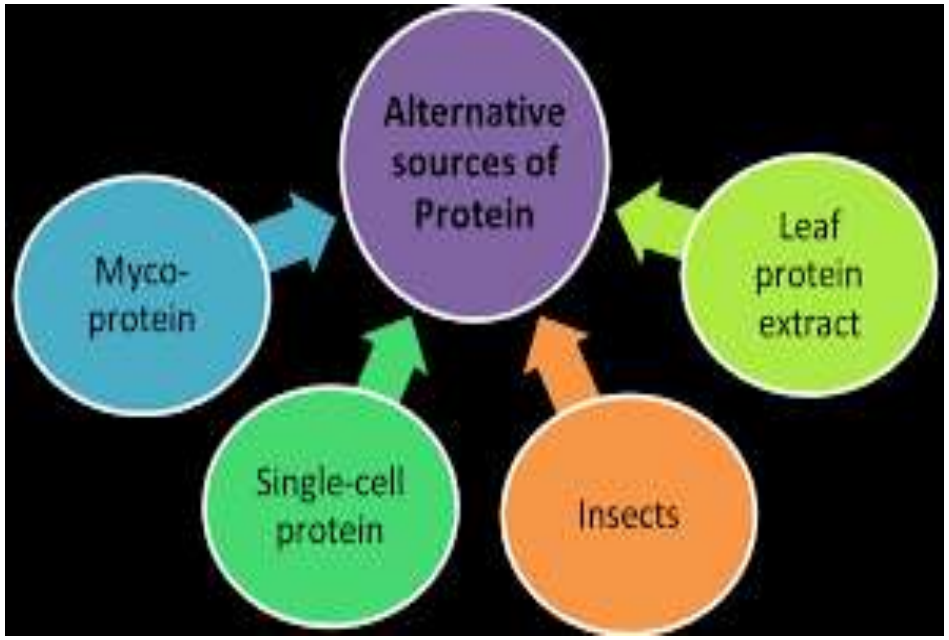
Epub 2016 Nov 2.

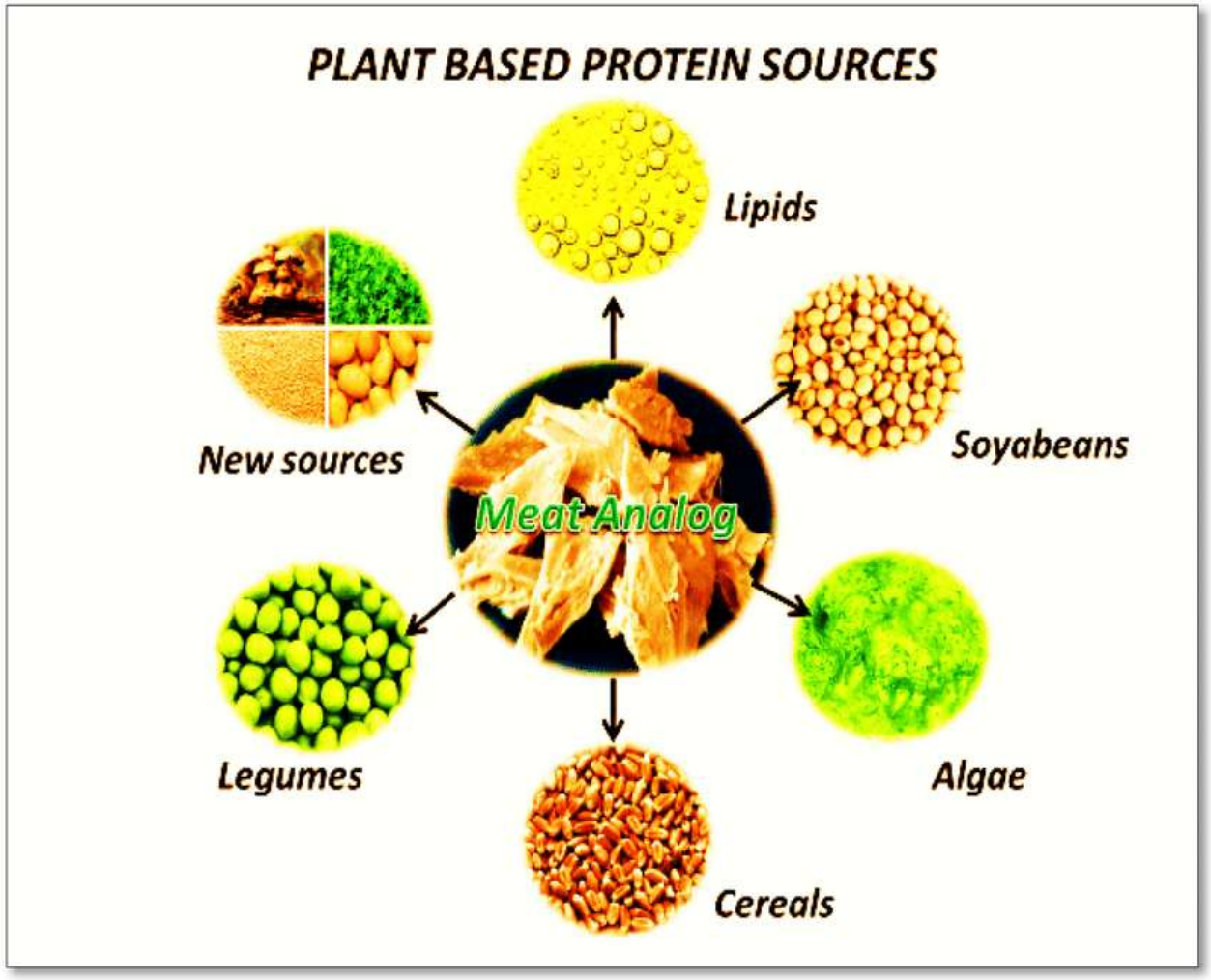
Physiological effects of epigallocatechin-3-gallate (EGCG) on energy expenditure for prospective fat oxidation in humans: A systematic review and meta-analysis

Mahendra P Kapoor [1], Masaaki Sugita [2], Yoshitaka Fukuzawa [3], Tsutomu Okubo [4]

Green tea catechins (GTCs) are known to improve fat oxidation (FOX) during fasted, rested and exercise conditions wherein epigallocatechin-3-gallate (EGCG) is thought to be the most pharmacologically active and has been studied extensively. From the available data of randomized controlled trials (RCTs) on EGCG, we carried out a systematic review and meta-analysis to elucidate whether EGCG consumption indeed increase energy expenditure (EE) and promote FOX. A systematic review of the literature was conducted using electronic databases (PubMed, Embase, Cochrane Library, CINAHL, JICST, JSTPLUS, and JMEDPLUS and others) and eight RCTs were included. RCTs were reviewed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and methodological quality was assessed. After data extraction, results were aggregated using fixed- and random-effect approaches and expressed to quantify the relationship between the dose of EGCG for respiratory quotient (RQ), EE and rate of FOX to compare the EGCG and placebo treatments. The meta-analysis results of verities of studies in terms of dose and length of duration revealed that EGCG supplementation provided significant mean difference (MD) when compared with placebo for RQ [MD: -0.02; 95% confidence intervals (95% CI), -0.04 to 0.00; I2=67%; P=.01] and EE [MD: 158.05 kJ/day; 95% CI, 4.72 to 311.38; I2=0%; P=.04] in fixed-effect approach. Changes in FOX did not reach the level of statistical significance. Meta-analyses of EGCG influence on the body mass index, waist circumference and total body fat mass (TBFM) were also examined and their impact on the promotion of FOX is reported. Effect of EGCG doses was also systematically reviewed. Finding showed that EGCG intake moderately accelerates EE and reduces RQ. The analyses revealed that the EGCG resulted in difference in RQ and EE but the effect on the other measures of energy metabolism was relatively mild. Possibly, EGCG alone has the potential to increase metabolic rate at 300 mg dose. Collectively, the outcome supports the findings that EGCG has an effect on metabolic parameters. However, the large prospective trials are needed to confirm the findings.

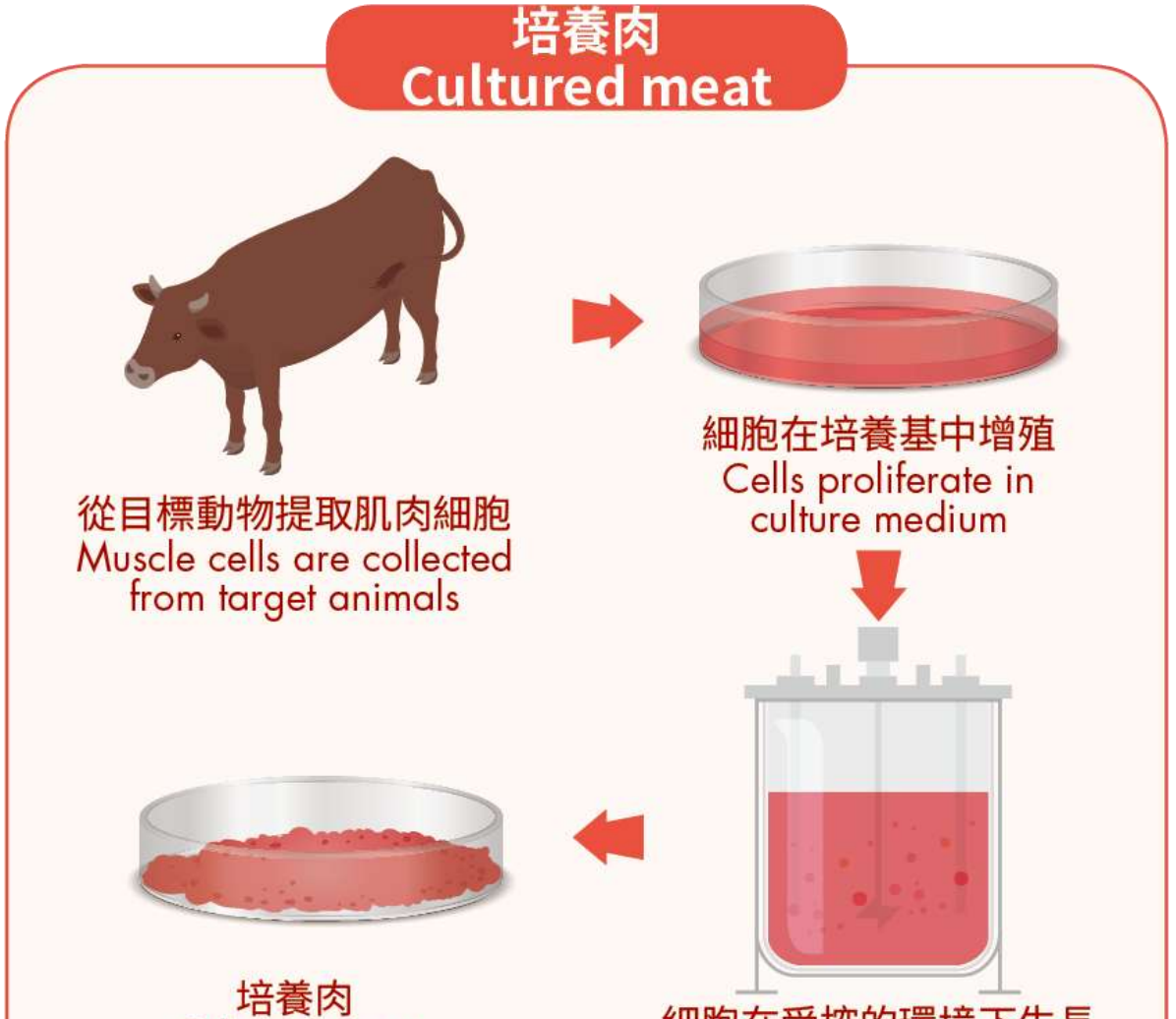
Novel Protein Sources



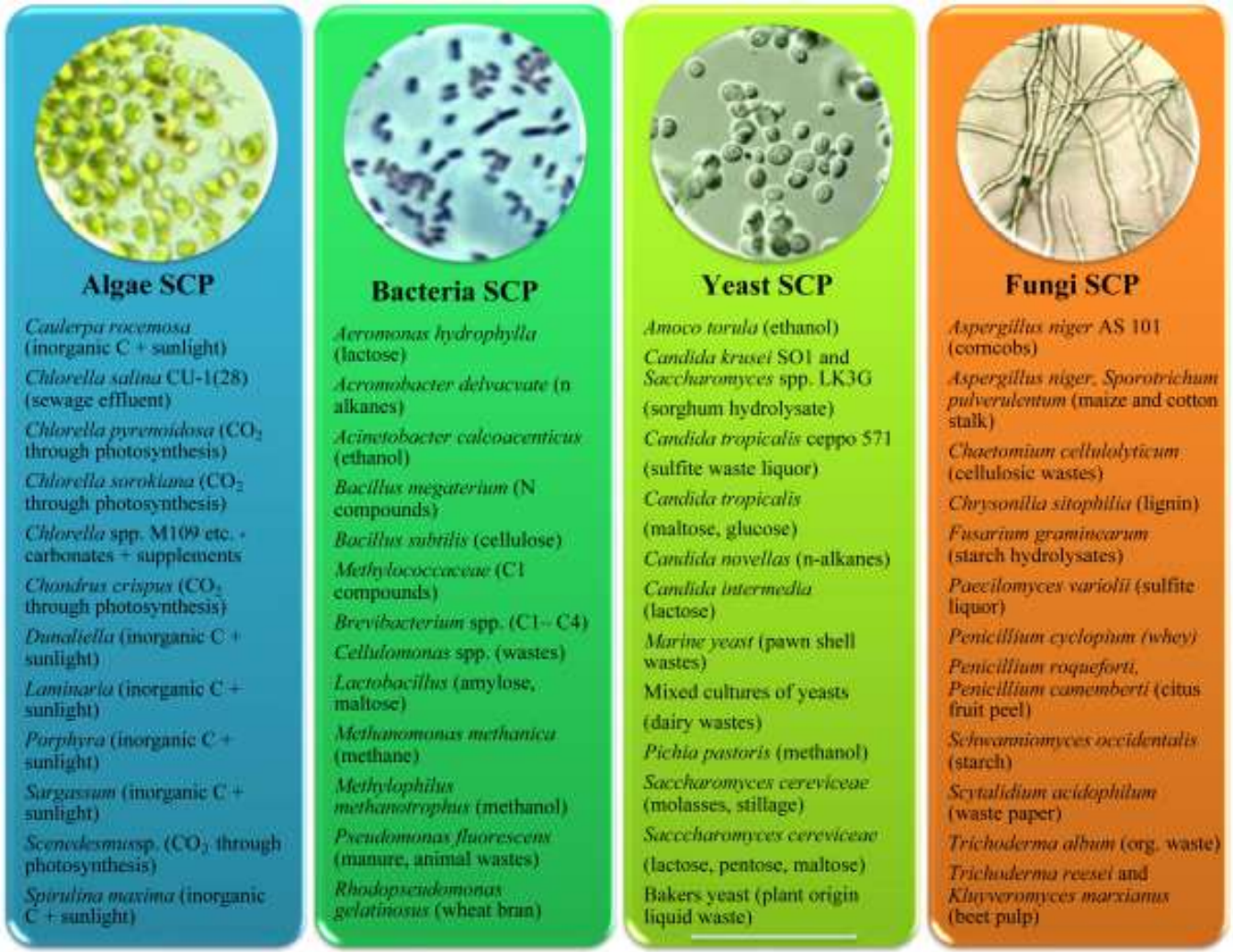


A mega market

Plant based meat: cultured meat



Proteins from microorganisms , single-cell proteins (SCPs)



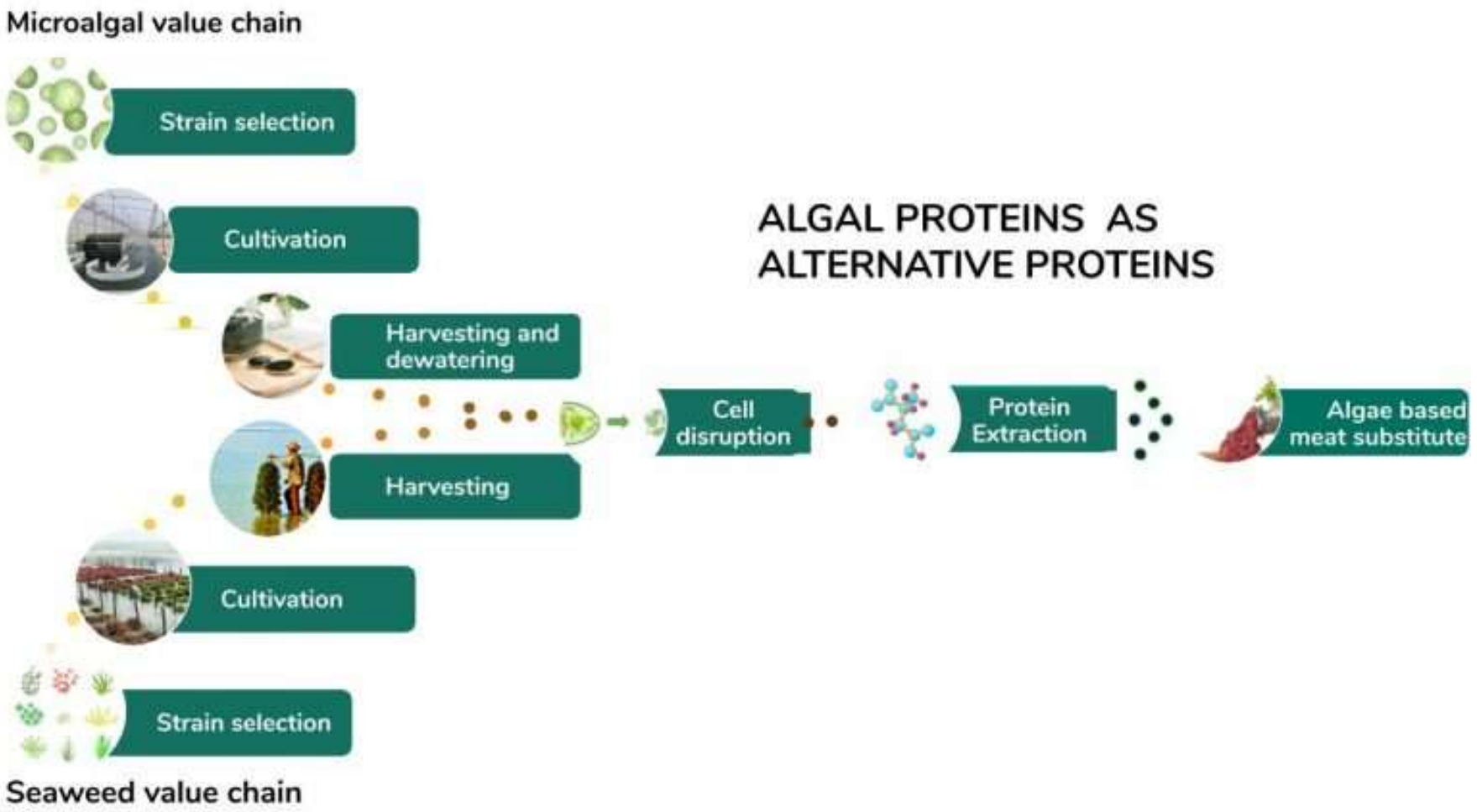
Single cell proteins

What is single cell protein??

- Single-cell protein (SCP) refers to crude or refined protein of algal, bacterial, mold, or yeast origin which is used either as animal feed or human food.

- The term single cell protein was introduced in the 1960s to describe protein-rich foods manufactured from yeasts that served as dietary supplements for livestock and humans.
- The production and utilization of microbial biomass as a source of food proteins gained particular interest as an alternative source for proteins of agricultural origin due to its high content of protein.
- Algae as a source of SCP is a term which refers to either microscopic single-cell true algae or prokaryotic cyanobacteria, and their growth is based on use of carbon dioxide and light energy.
- Quorn is produced from a multi-cellular, filamentous fungus, the term single cell protein is inaccurate and **mycoprotein** is the preferred name.
- **Mycoprotein** is a form of single-cell protein, also known as **fungal protein** "Protein derived from fungi, especially as produced for human consumption.

Protein (and other goodies) from algae



Algae as human food

- Algae have been used as human food for thousands of years in all parts of the world.
- The most commonly consumed macro algae include the
  1. Red algae Porphyra(nori, kim, laver)
  2. Asparagopsis taxiformis(limu)
  3. Chondrus crispus(Irish moss)
  4. Kelps Laminaria(kombu)
  5. Palmaria palmata(dulse)
  6. Macrocystis
  7. Undaria(wakame)
  8. Green algae Caulerpa racemosa
  9. Codium

Plant-based proteins

- Made from soy, peas, lentils, wheat, or other proteins mixed with ingredients such as oils
  - Binding agents such as methylcellulose may be added
- May be called “meat analogues”, “veggie burgers”
- Some products have been formulated to “bleed” like meat
  - Impossible™ burger uses genetically engineered soy leghemoglobin
  - Beyond Meat® uses beet juice

Microalgae as a novel food

Potential and legal framework

Tomke F. Prüser, Peggy G. Braun, Claudia Wiacek

Abstract

Microalgae such as *Chlorella* and spirulina have high dietary potential, because they contain a large number of nutrients which seem to make them predestined for use in human nutrition. They are characterised by fast growth and enable low-resource production of important nutrients, such as n-3 fatty acids.

Alongside a few approved species of microalgae, there are several thousand microalgae that are not used in human nutrition despite their interesting nutrient profile. The reasons for this are explored in this outline paper and can be traced back to Europe's legal framework for consumer protection. As a result of the Regulation on novel foods, foods are only approved for use on the European market after a time-consuming investigation process, in order to protect consumers from unsafe foodstuffs.

Keywords: microalgae, novel food, Novel Food Regulation, n-3 fatty acids, vitamin B_{12}

Microalgae

The name "algae" is a collective term for a large polyphyletic group of living things including both plants and bacteria. What they almost all have in common is that they contain chlorophyll and are thus also able to produce energy from light, carbon dioxide and water through oxygenetic photosynthesis [1]. They differ from mosses and ferns in that algae are not specialised for life on land [2]. Even this very general definition is incomplete and excludes whole taxa of algae which have lost the ability to photosynthesise over the course of their development [1, 2].
The algae group is divided into microalgae and macroalgae, whereby macroalgae are multi-

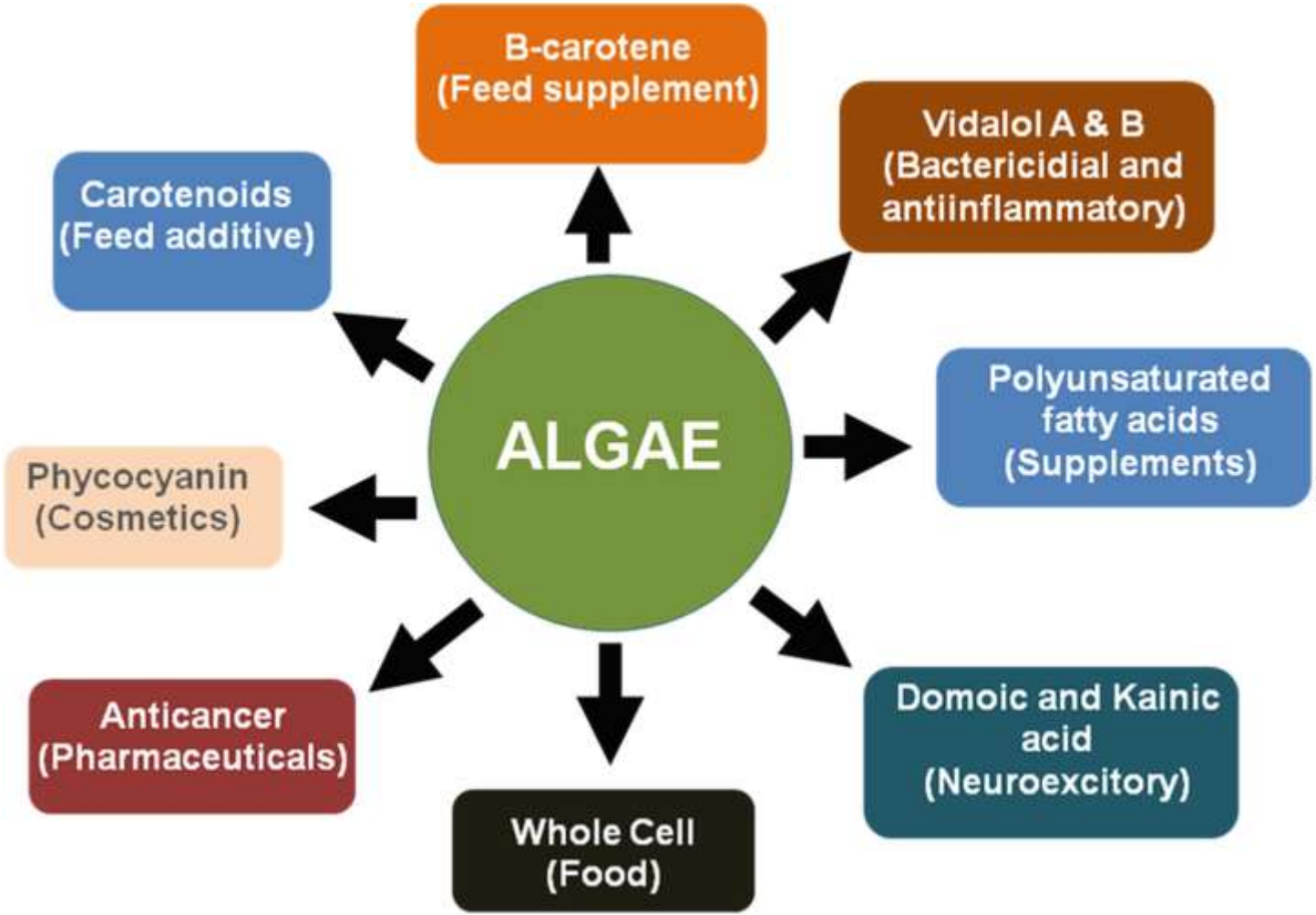
Molke

Microalgae in the food industry

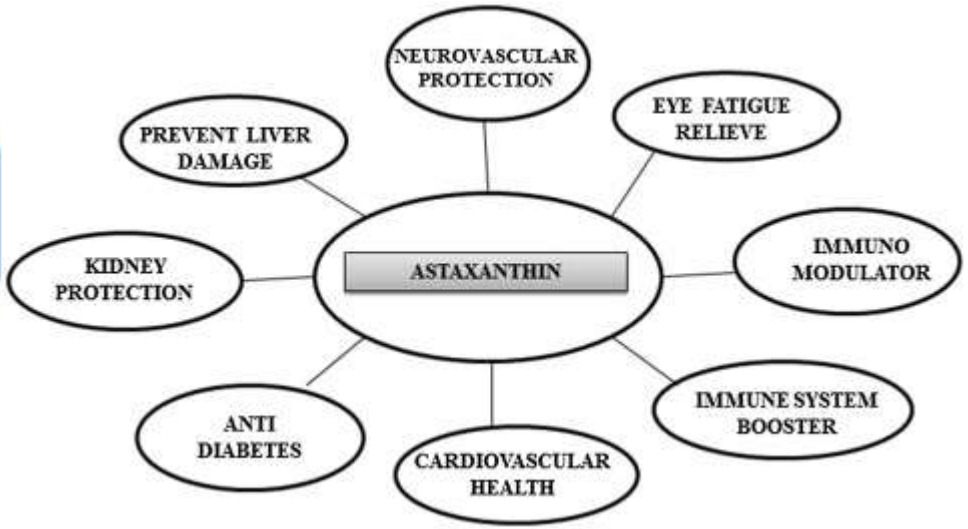
Microalgae such as *Chlorella* and spirulina have considerable dietary potential due to their spectrum of nutrients. They thus became a focus of research as early as 1950 and the first microalgae were cultivated and marketed on a commercial scale from 1960 [8]. Since then interest in microalgae has steadily increased due to their adaptability and the number of different constituents which can be obtained from them [8, 11]. Whereas initially microalgae were sold mainly as nutritional supplements in the form of powders, capsules, and tablets, today they are also incorporated into various products like pasta, smoothies, soft drinks, chocolate, and ice cream [12, 13]. In 2018 the global market volume for microalgae products was already USD 9.9 billion and with a projected annual growth rate of over 7% market volume could reach USD 14.99 billion by 2024 [14]. There are large production plants in countries such as Israel, United States, Australia and China. In Germany too there are at least 13 plants producing microalgae [15].

Spirulina is promoted mainly for its protein and vitamin B12 content. Tablets of dried spirulina have a vitamin B12 content of 120–240 µg/100 g, although 83% is in the form of non-bioavailable pseudovitamin B12 [17]. The protein content in spirulina is around 50–60% of the dry mass with a biological value of 50–70 [18]. However, even microalgae not approved up to now have major potential. For instance, not only does the dry mass of Phaeodactylum tricornutum contain 1.7-5.0% of eicosapentaenoic acid (EPA) [29], it also contains the carotenoid fucoxanthin

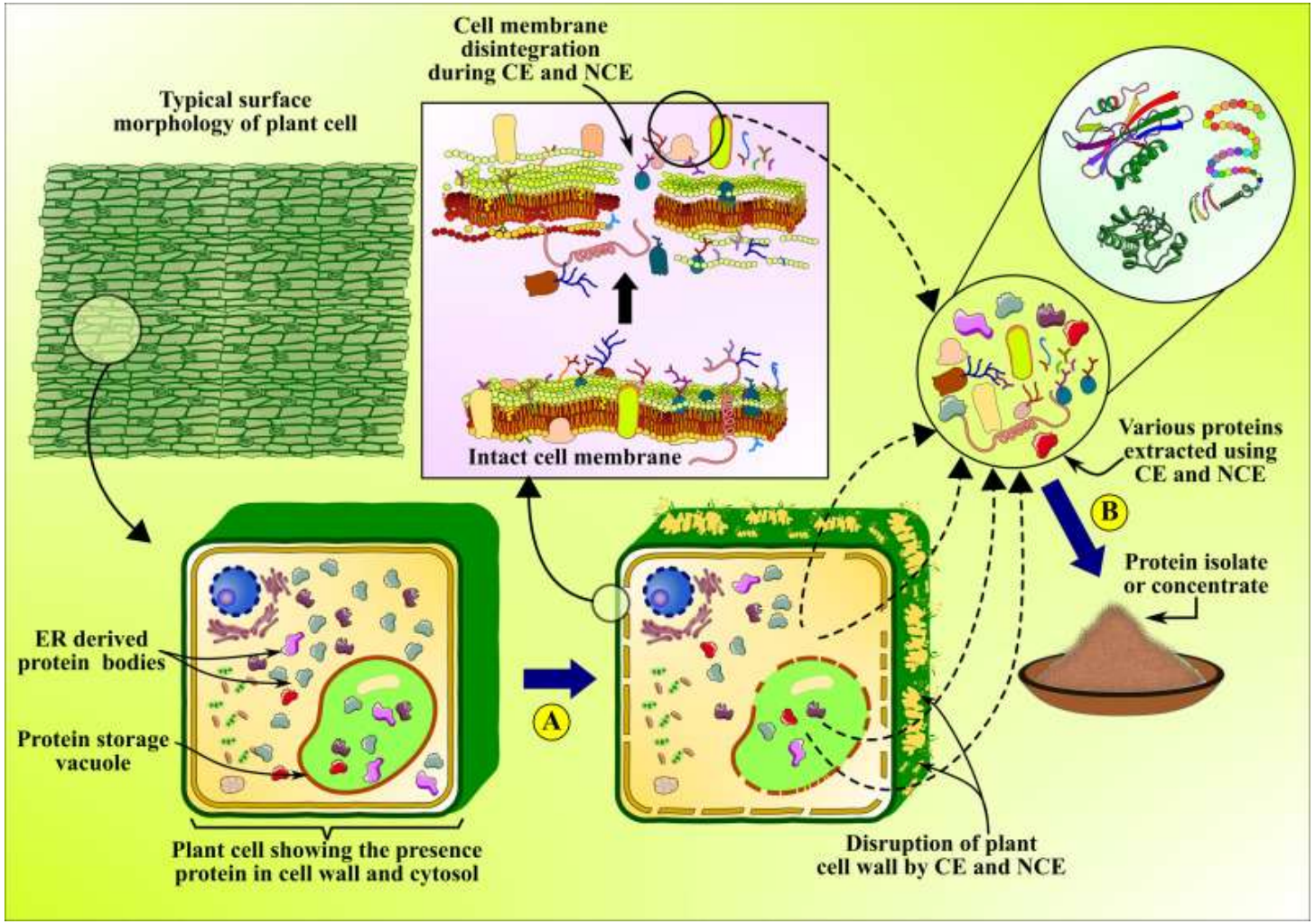
Goodies from algae



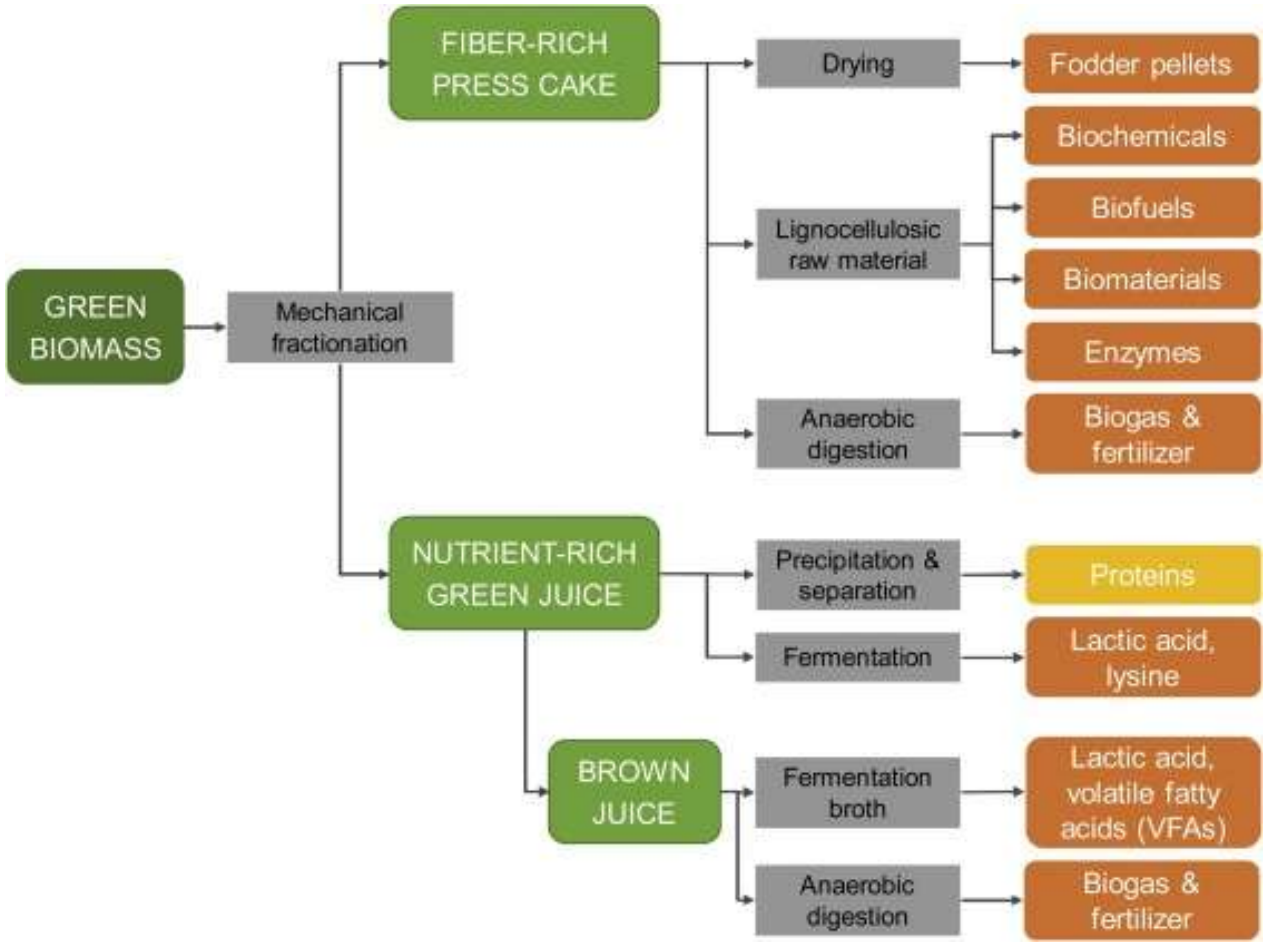
Astaxanthin is produced naturally in the freshwater microalgae Haematococcus pluvialis and the yeast fungus Xanthophyllomyces dendrorhous

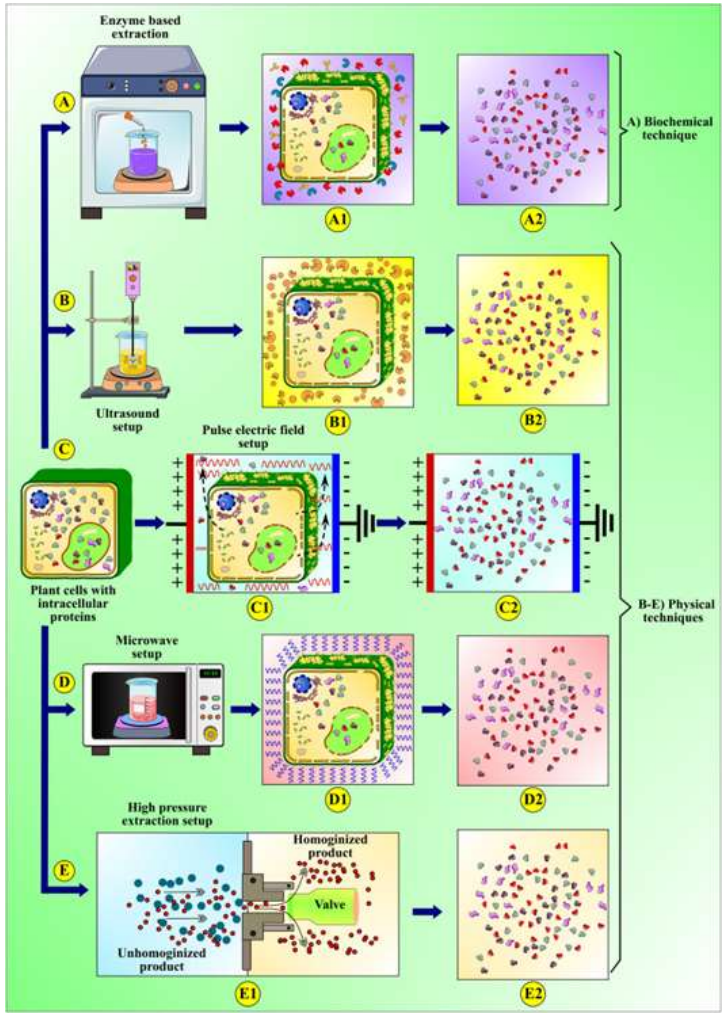


Plant protein sources, non-conventional extraction techniques (NCE)



Plant protein sources, methods





Plant-based proteins- 2

Regulation: FDA regulates

- Daily regulation not required
- Food processors must have risk-based preventive food safety system in place
- Discussion in many states and federal level on what can be called a “burger”, “sausage”, “meat” or similar terms

EU Novel food ?

Plant-based proteins- 3

- Food safety considerations: consumers with allergies to wheat, soy, etc should check label
  - Cook to 165F, use same good practices as with meat
- Marketplace status: Available in many restaurants and grocery stores

Plant-based proteins- nutrition comparison

- Slightly different than meat

Table 1. Nutritional comparison of a regular Whopper® to an Impossible™ Whopper® (patty only)

	Regular Whopper®	Impossible™ Whopper®
Calories (Kcal)	240	210
Fat (g)	18	12
Saturated Fat (g)	8	7
Trans Fat (g)	1.5	0
Cholesterol (mg)	80	0
Sodium (mg)	230	330
Carbohydrates (g)	0	9
Fiber (g)	0	2
Sugar (g)	0	1
Protein (g	20	17

Further nutrition considerations

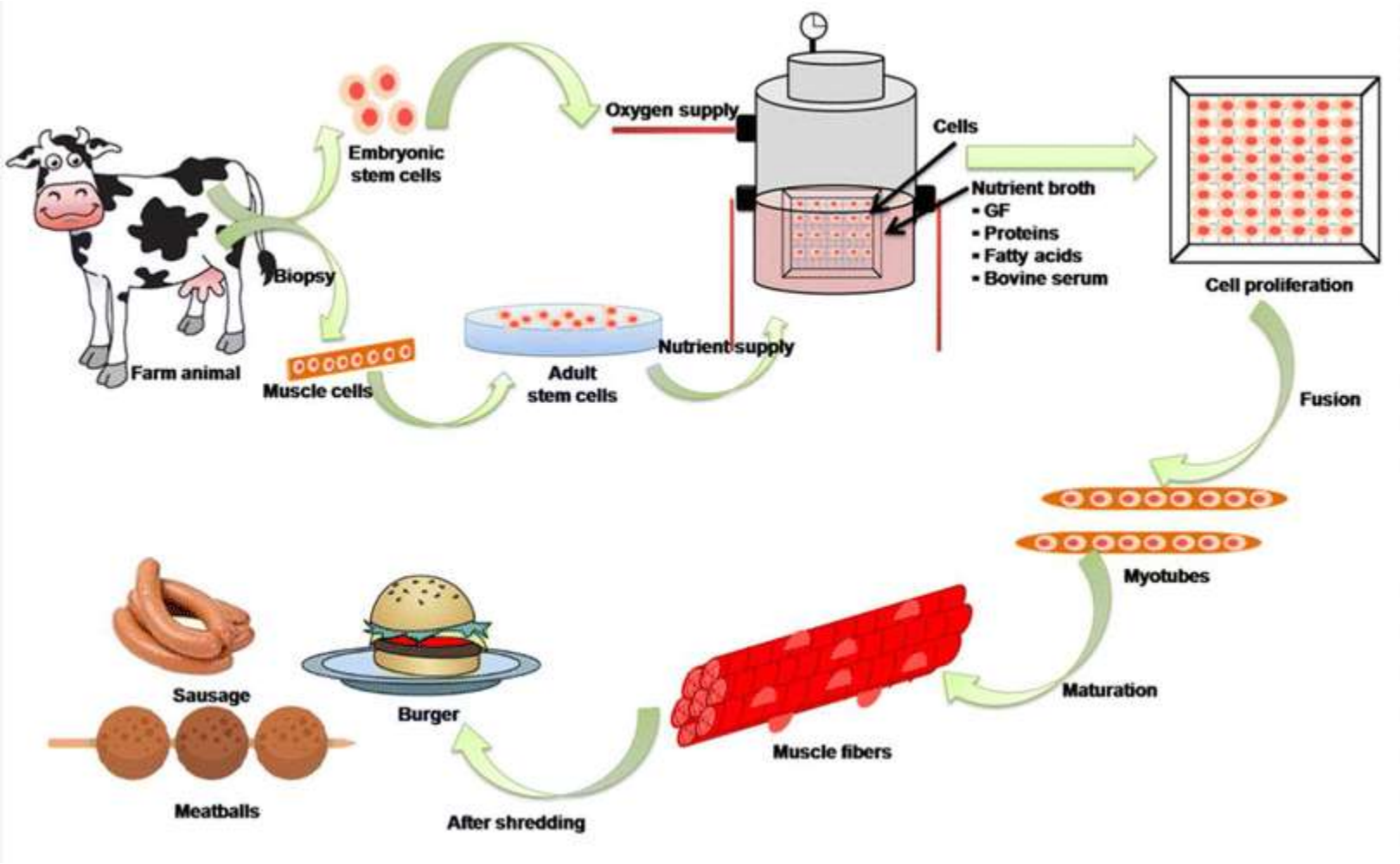
- Noted nutrients likely lacking in most beef replacements and meat replacements include:
  - Monounsaturated fatty acids
  - Vitamins B_3 (niacin), B_{12}*
  - Zinc
  - Choline
  - Selenium

  *Lack of B_{12} represents a well-known and potentially serious limitation of plant based diets

Cultured meat is coming

- NOT currently available for many consumers
  - Not currently produced on large scale
- Grown in laboratories from animal cells in culture medium
  - Grown on an edible non-meat scaffold that holds cells in position
- May be called “cultured protein”, “clean meat”, “lab-grown meat”, “in vitro meat”, others

Cultured meat, production



There are three stages in the production of cultured meat.

1. Selection of starter cells,
2. Treatment of growth
3. Scaffolding,

Cells, media, scaffolds (Gerüst)

- To collect cells that have rapid rate of proliferation.
- Stem cells does not develop toward a specific kind of cells. So cells such as myosatellite and myoblast cells are often used.
- Because the cells will helps in producing a structural cells.

- Cells are then treated by applying a solution that promotes tissue growth known as growth medium.
- Medium should contain necessary nutrients and appropriate quantities of growth factor.
- Then they are placed in a bioreactor which is able to supply the cells with energetic requirements.
-
- To cultured 3 dimensional meat, the cells are grown on scaffold.
- The idea scaffold is edible so meat does not have to be removed and periodically moves to stretch the developing muscle.
- Scaffold must maintain flexibility in order to not detach from developing myotubes.
- Scaffold d must allow vasucularization (creation of blood vessel) in order to develop normal muscle tissue.

3D printing ?

- Additive manufacturing:

An Israeli company Meatech proposes to use 3 dimensional printing techniques to improve the texture of cultured meat.

- Sacffold based production technique can be only appropriately used in boneless or ground meats.
- End result of this process would be meat for hamburger and sausages.

Alternative proteins EU Novel Food law and FDA

Highlights

- EU food law impacts the transformative potential of alternative proteins.
- Insects and cultured meat are novel foods; several microalgae and macroalgae are not.
- The GM Food Regulation applies to all genetically modified or edited foods.
- The names of vegan products have caused controversy.
- The principles of non-discrimination and proportionality are important for fairness.

The Novel Food Regulation focuses on the nutritional and food safety concerns with human foodstuffs, and in microbial proteins the main food safety concerns are the high RNA content, toxic metabolites and contamination of the microbial cultures with other microorganisms (Ritala et al., 2017). T

The biomass produced by cellular agriculture may be harvested and processed for food as such, or its proteins may be extracted to produce a pure protein isolate.

Protein extraction may cause significant changes to the nutritional content of the raw material and the resulting protein isolate may thus be considered a novel food, although the production organisms itself would not fall under Novel Food Regulation (Regulation (EU) 2015/2283

Table 1. **Microorganisms accepted as food in the EU**. *Consumed in EU countries before 1997.

Scientific name	Common name	Organisms	Legal status	Reference
Aphanizomenon flos-aquae	AFA	Cyanobacterium	Not novel*	EU Novel Food Catalogue
Spirulina sp.	Spirulina	cyanobacterium	Not novel*	EU Novel Food Catalogue
Arthrospira platensis	Spirulina	cyanobacterium	Not novel*	EU Novel Food Catalogue
Chlorella luteoviridis	Chlorella	microalga	Not novel*	EU Novel Food Catalogue
Chlorella pyrenoidosa	Chlorella	microalga	Not novel*	EU Novel Food Catalogue
Chlorella vulgaris	Chlorella	microalga	Not novel*	EU Novel Food Catalogue
Odontella aurita		microalga	Authorized novel food, for use as small quantities in specified food products	(EU) 2017/2470
Tetraselmis chuii		microalga	Authorized novel food, small quantities in specified food products and as food supplements	(EU) 2017/2470
Saccharomyces cerevisiae	Brewer's yeast, budding yeast	microfungus, yeast	Not novel*	
Fusarium venenatum		microfungus	Not novel*	Wiebe (2004)
Yarrowia lipolytica		microfungus, yeast	Authorized novel food, only for use in food supplements	(EU) 2017/2470
Clostridium butyricum		bacterium	Authorized novel food, only for use in food supplements	(EU) 2017/2470

Proteins from arthropods, insects

Insekten als Lebensmittel

- in über 200 Ländern als Lebensmittel verzehrt
- v.a. in Asien, Afrika, Lateinamerika

- in Kenia und Thailand

-> Massenzüchtungen

- in westlichen Ländern Säugetiere als Hauptproteinquelle -> kaum Insektenverzehr

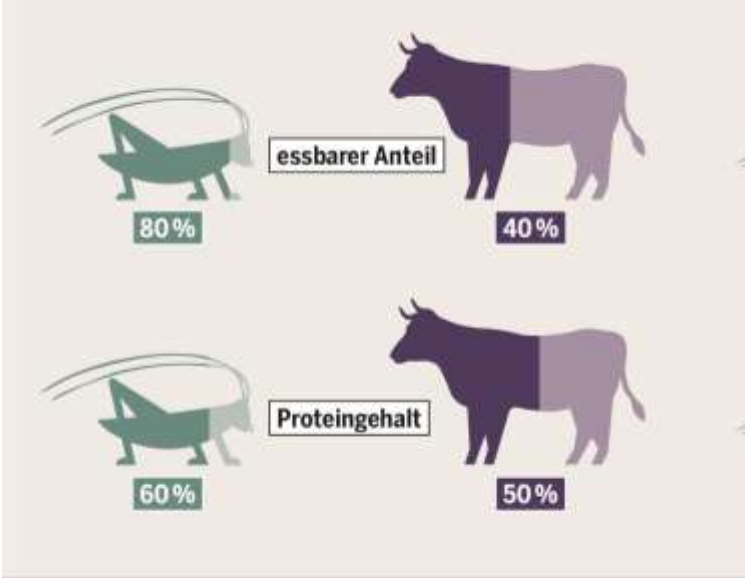
[Garino et al., 2019]

https://katapult-magazin.de/de/artikel/artikel/fulltext/esst-mehlwuerme

Gesundheitliche Vorteile von Insekten

- vergleichbare Nährstoffgehalte wie Fleisch und Fisch

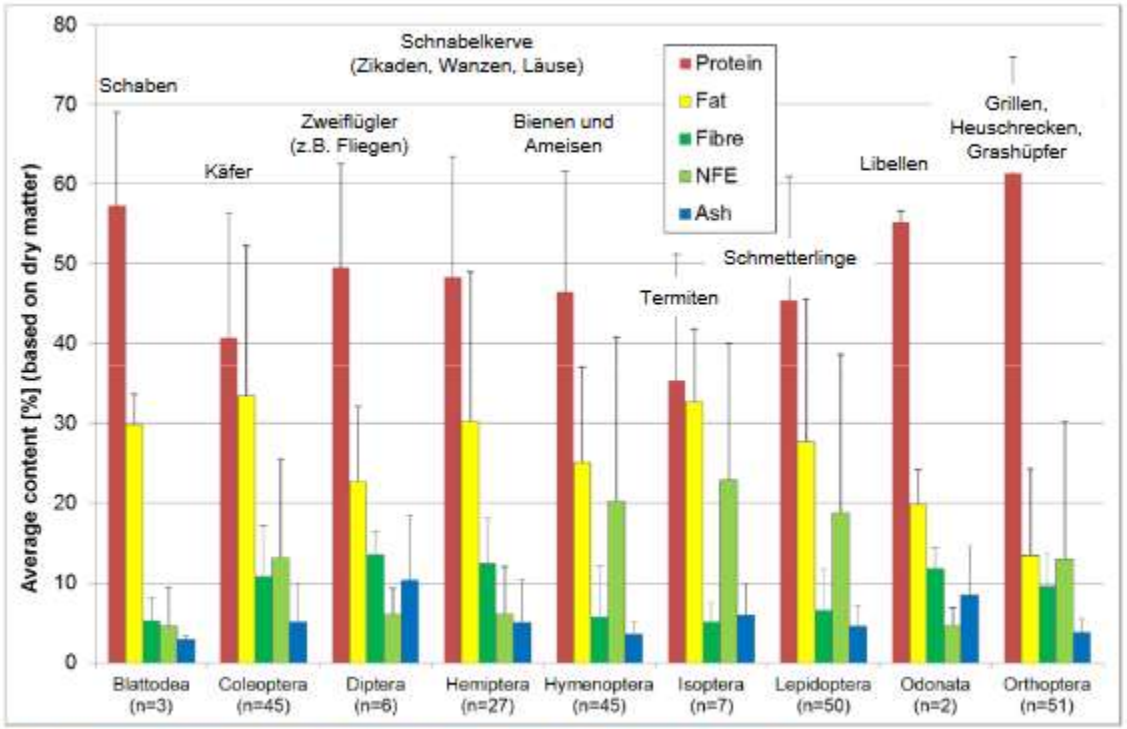
- **hohe Gehalte an:**
  - essentielle Aminosäure
  - mehrfach ungesättigten Fettsäuren
  - Ballaststoffen
  - Mineralstoffen: Kupfer, Eisen, Magnesium, Mangan, Phosphor, Selen und Zink



[1]

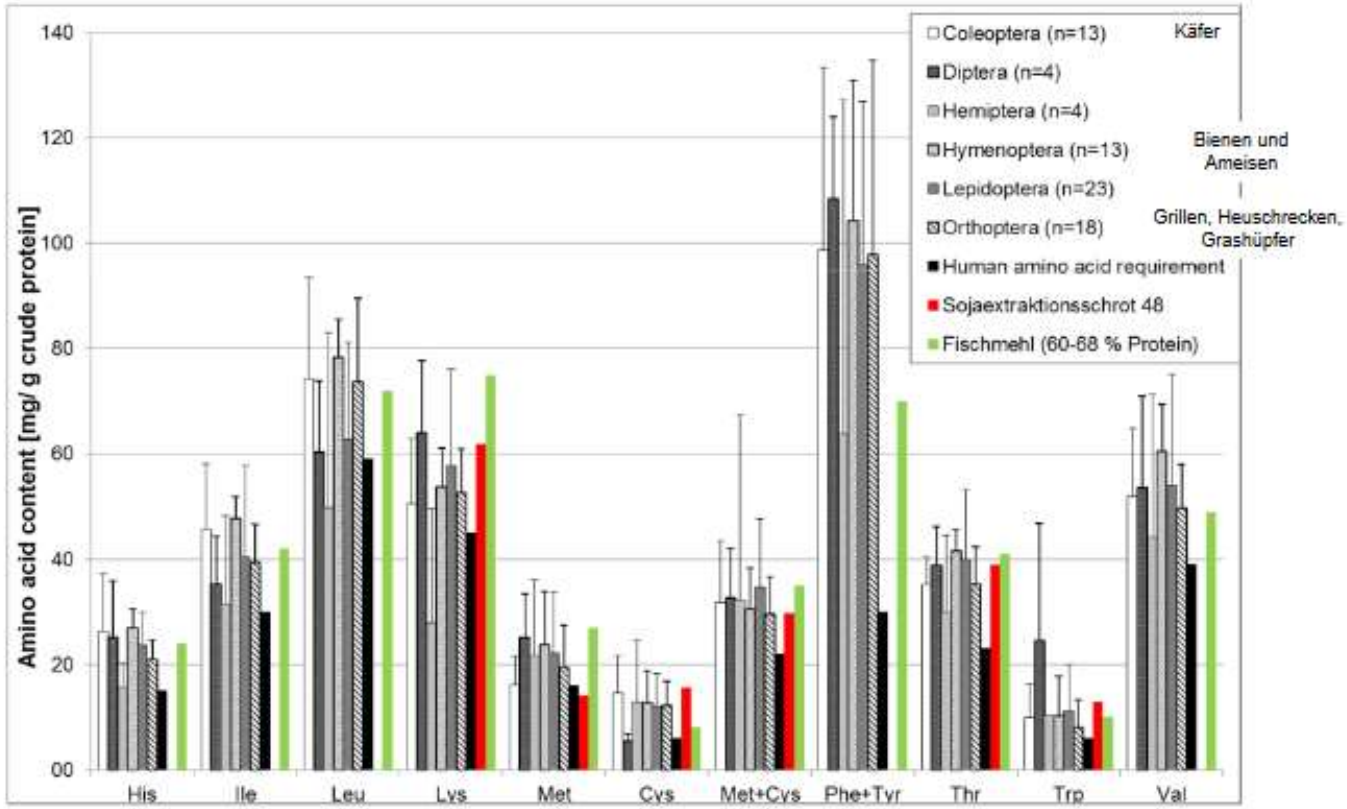
[FAO, 2013]

Durchschnittliche Zusammensetzung verzehrter Insekten



(n = Datenmenge; NFE – nitrogen-free extract (Kohlenhydrate);

Aminosäurespektren verzehrter Insekten



[BfR, 2016]

ökologische und ökonomische Vorteile

- geringer Futter und Wasserverbrauch

 -> effizientere Futterverwerter

  -> 2kg Futter ≙ 1kg Insektenmasse

  -> 8kg Futter ≙ 1kg Rindermasse

- weniger Landverbrauch
- geringer Treibhausemissionen

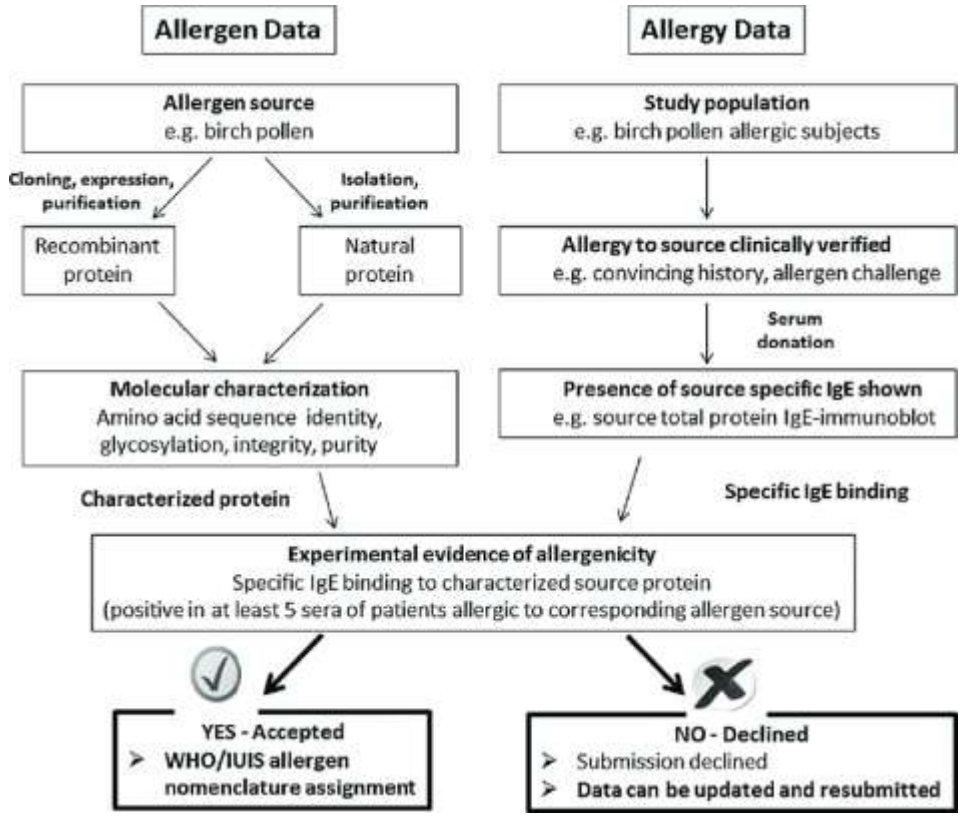
[1]

- Zucht auch mit geringen Ressourcenaufwand möglich

-> auch für Schwellen- und Entwicklungsländer

[FAO, 2013]

Main problem allergy in all novel protein sources



Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, January, 2001

- ***"6.1. Sequence Homology as Derived from Allergen Databases***
- The commonly used protein databases (PIR, SwissProt and TrEMBL) contain the amino acid sequence of most allergens for which this information is known. However, these databases are currently not fully up-to-date. A specialized allergen database is under construction.
- *Cross-reactivity between the expressed protein and a known allergen (as can be found in the protein databases) has to be considered where there is: 1) more than 35% identity in the amino acid sequence of the expressed protein (i.e. without the leader sequence, if any), using a window of 80 amino acids and a suitable gap penalty (using Clustal-type alignment programs or equivalent alignment programs) or: 2) identity of 6 contiguous amino acids.*
- If any of the identity scores equals or exceeds 35%, this is considered to indicate significant homology within the context of this assessment approach. The use of amino acid sequence homologies to identify prospective cross-reacting allergens in genetically-modified foods has been discussed in more detail elsewhere (Gendel, 1998a, Gendel, 1998b).

Risiko allergenes Potential

- direkte Allergie bei Mehlwürmern und Seidenraupe
- Kreuzreaktivität bei Hausstaubmilben- und Meeresfruchtallergikern zu Tropomyosin und Argininkinasen der Insekten

  -> bei Mehlwürmern, Grillen, Grashüpfer, Motte, Termiten, Schabe

Vorkommen:

- 7,6% allergische Reaktionen
- davon 18% anaphylaktischer Schock

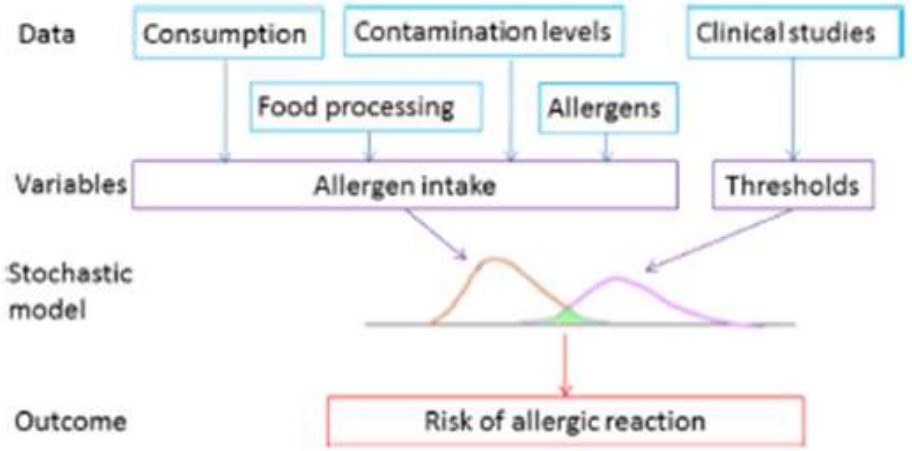
Symptome:

Hautreaktionen (Rötung, Urticaria), GI-Probleme (Bauchschmerzen, Diarrhoe), respiratorische Störungen (Asthma, Dyspnoe)

[De Gier & Verhoeckx, 2018]

Risikoanalyse-System allergenes Potential

- Verhinderung einer Übertragung von allergenen Material auf andere Lebensmittel
  -> Schutz von Allergikern



- Stellung eines Novel Food- Antrags
  -> Beweis, dass kein allergenes Protein in Lebensmittel enthalten
  -> Vergleich der AS-Sequenz mit Sequenz von allergenen Proteinen

[Garino et al., 2019]

Risikoanalyse-System Allergene (Mehlwürmer)

1. **Stufe: Gefahrenidentifikation**
   -> allergische Reaktionen durch Hautkontakt, Inhalation oder Verdauung
   -> IgE-Körper Produktion

2. **Stufe: Gefahrencharakterisierung**:
   -> Bestimmung Grenzwert-Dosis für allergische Reaktion (durch klinische Studie)
   -> Effektive Dosis (5%, 10%, 50%)

3. **Stufe: Aufnahme Beurteilung**:
   -> Menge von konsumierten Produkt
   -> Konzentration Allergen in Produkt
   -> Wahrscheinlichkeit, dass allergenes Produkt aufgenommen wird
   -> Charakterisierung und Prävalenz von klinischen Subgruppen

4. **Stufe: Risiko Charakterisierung**
   -> Charakterisierung des Risikos bei verschiedenen Leveln von Allergenen
   -> Entwicklung eines sicheren Grenzwertes für allergene LM

[Garino et al., 2019]

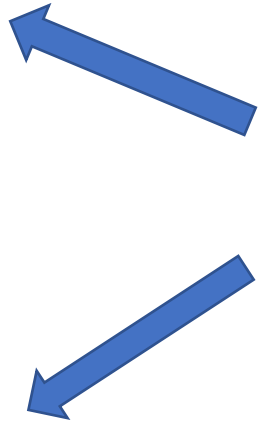
Risiko: biologische und chemische Gefahren

Biologische Gefahren

- pathogene Bakterien
- Mykotoxin-produzierende Pilze
- Parasiten
- Viren
- Antibiotika resistente Gene

Chemische Gefahren

- Schwermetalle
- toxisch-chemische Verbindungen



Abhängig von:

- Spezifische Produktionsmethoden
- Substratverwendung
- Phase der Ernte
- Insektenspezies
- Verarbeitungsmethoden

[Garino et al., 2019]

gesetzliche Regelungen

- EU Regulation 2015/2283: Insektenbasierte Lebensmittel gehören zu Novel Food

- EU Regulation 2017/893: Liste mit 7 erlaubten Insektenspezies

  - Hermetia illucens (Soldatenfliege)
  - Musca domestica (Stubenfliege)
  - Tenebrio molitor (Mehlkäfer)
  - Alphitobius diaperinus (Getreideschimmelkäfer)
  - Acheta domesticus (Hausgrille)
  - Gryllodes sigillatus (Kurzflügelgrille)
  - Gryllus assimilis (Steppengrille)

Nachweismethode Insekten

- Für Gen-Identifikation C01-Gen verwendet

-> Cytochrom C Oxidase 1-Gen in Mitochondrien aller Tierarten

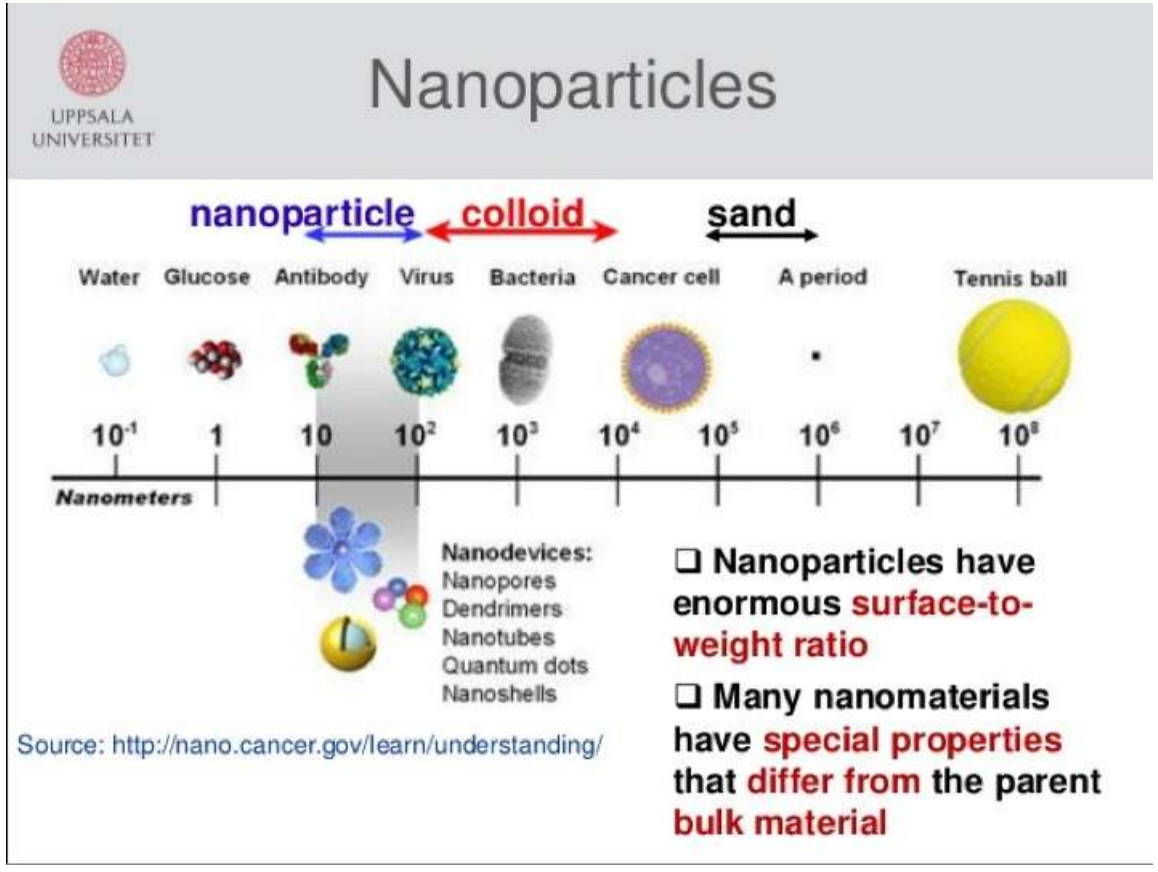
- C01-Gensequenz bei allen Spezies unterschiedlich
- je näher verwandt, desto ähnlicher

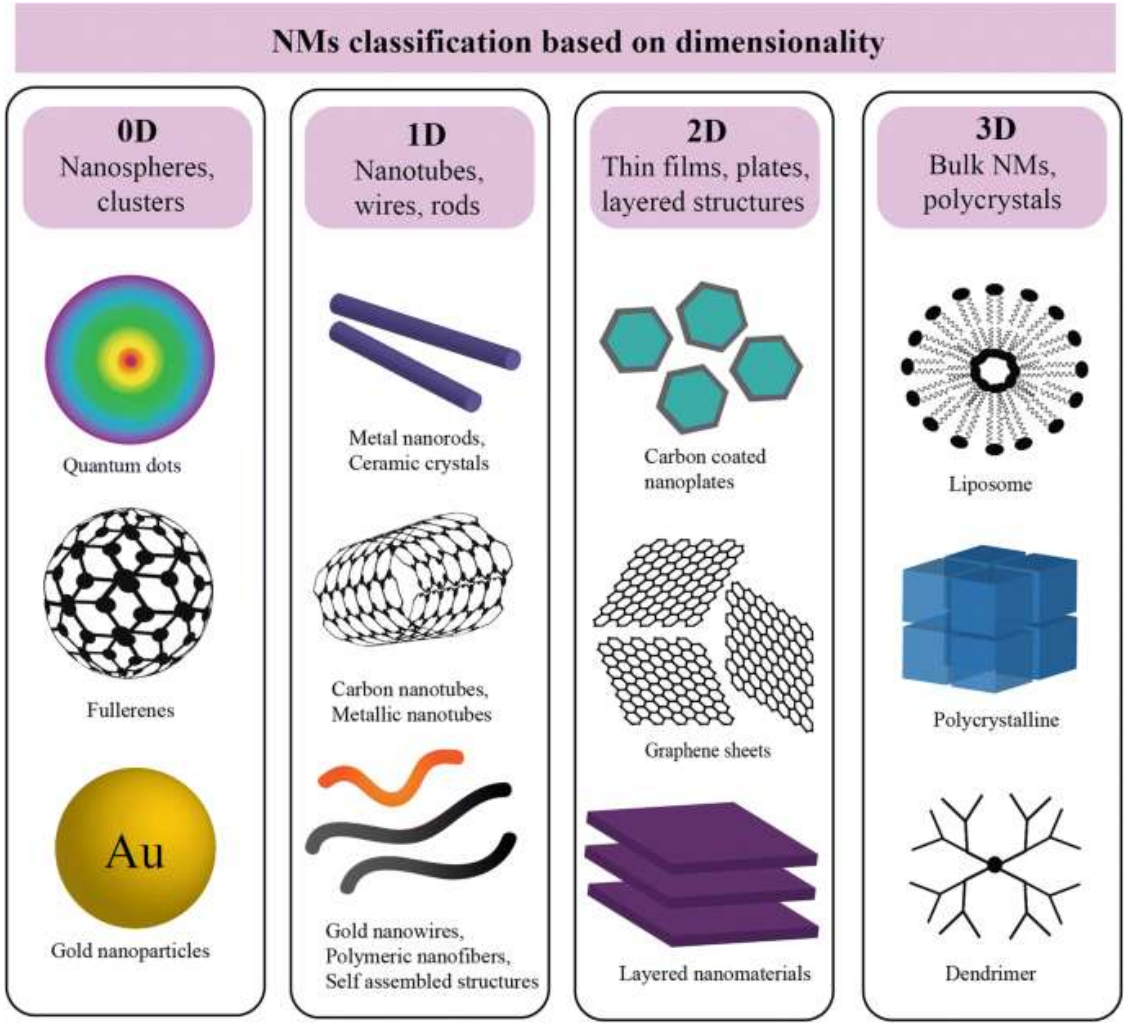
- Gensequenzen erlaubter Insektenspezies in Datenbank „Barcode of Life Data System (BOLD)" gespeichert

⇒ Nachweis durch Vergleich Gensequenz von Probe mit Datenbank

[Garino et al., 2019]

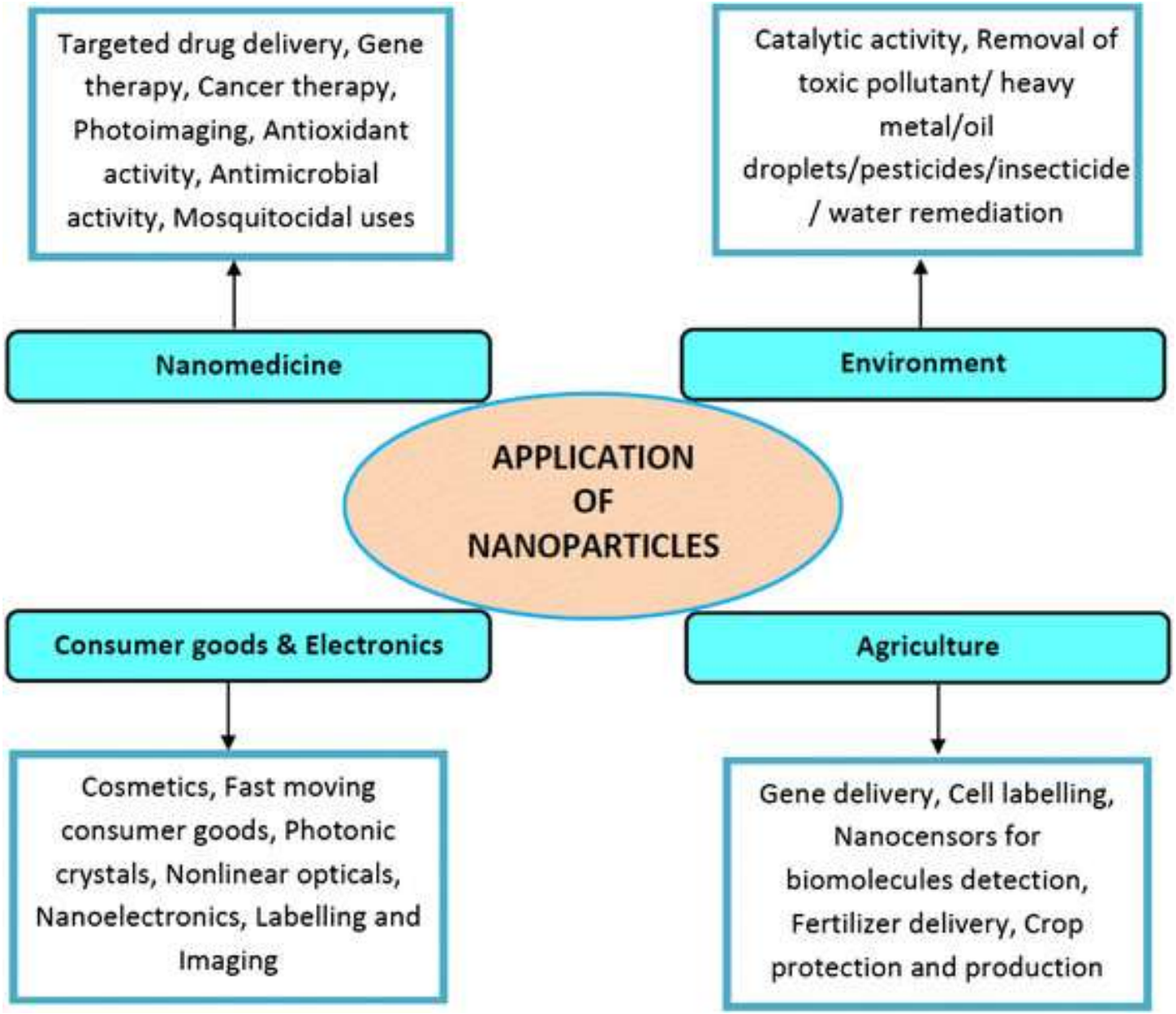
NANO particles, nutrition and foods

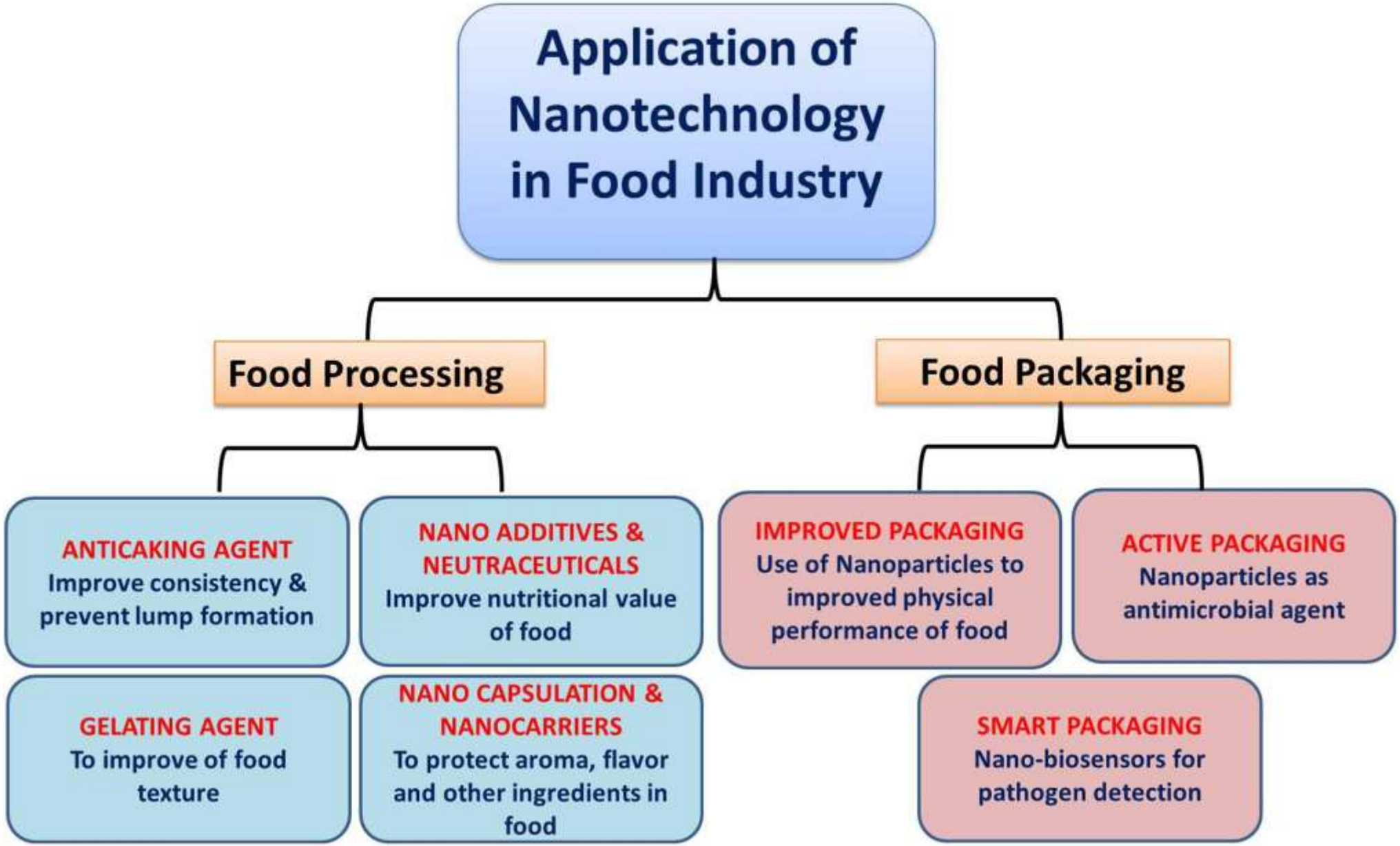




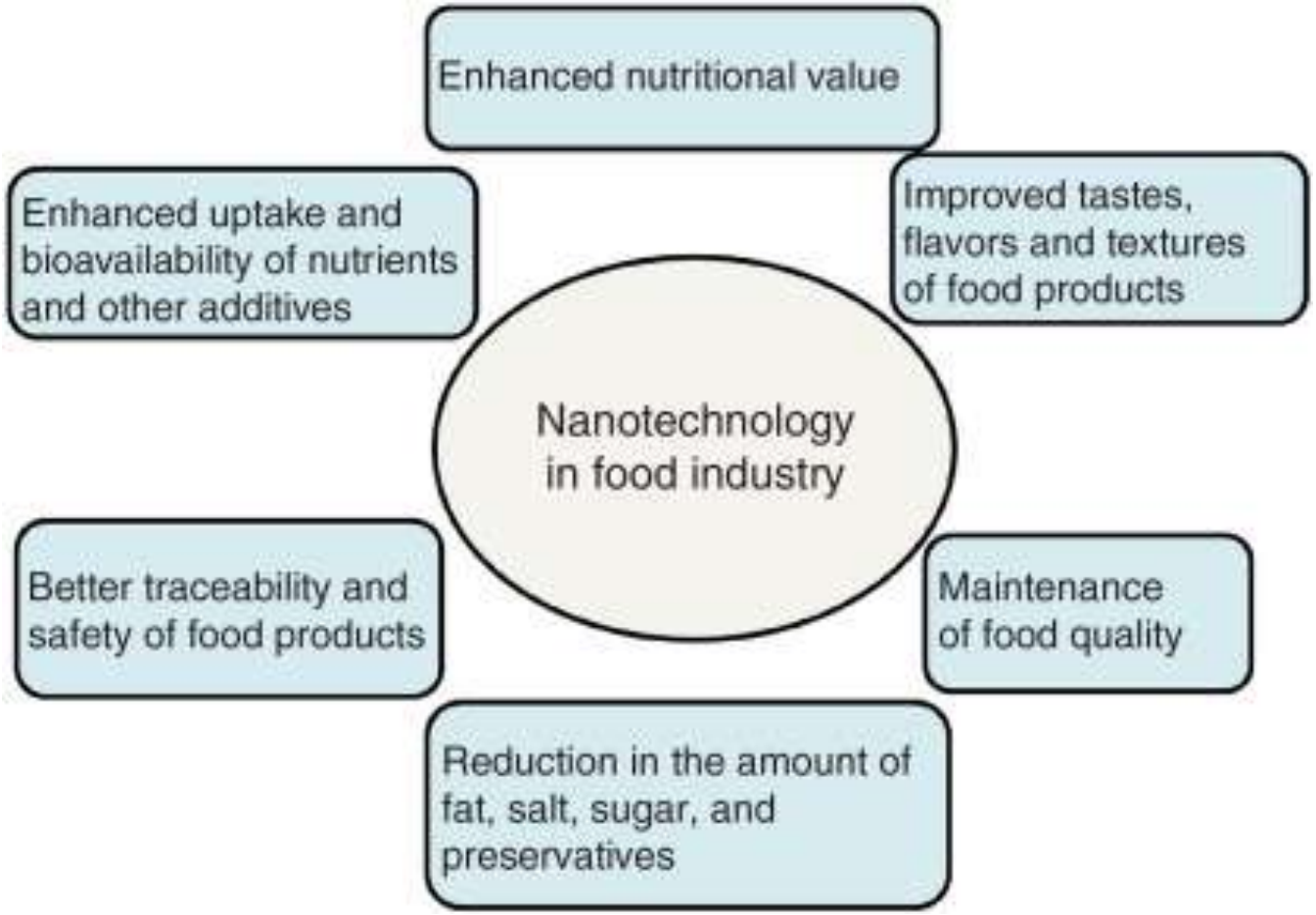
Quantum dots (QDs) are semiconductor particles a few nanometres in size, having optical and electronic properties that differ from larger particles due to quantum mechanics

Agriculture	Food Processing	Food Packaging	Supplements
• Single molecule detection to determine enzyme/ substrate interactions • Nanocapsules for delivery of pesticides, fertilizers and other agrichemicals more efficiently • Delivery of growth hormones in a controlled fashion • Nanosensors for monitoring soil conditions and crop growth • Nanochips for identity preservation and tracking • Nanosensors for detection of animal and plant pathogens • Nanocapsules to deliver vaccines • Nanoparticles to deliver DNA to plants (targeted genetic engineering)	• Nanocapsules to improve bioavailability of neutraceuticals in standard ingredients such as cooking oils • Nanoencapsulated flavor enhancers • Nanotubes and nanoparticles as gelation and viscosifying agents • Nanocapsule infusion of plant based steroids to replace a meat's cholesterol • Nanoparticles to selectively bind and remove chemicals or pathogens from food • Nanoemulsions and –particles for better availability and dispersion of nutrients	• Antibodies attached to fluorescent nanoparticles to detect chemicals or foodborne pathogens • Biodegradable nanosensors for temperature, moisture and time monitoring • Nanoclays and nanofilms as barrier materials to prevent spoilage and prevent oxygen absorption • Electrochemical nano-sensors to detect ethylene • Antimicrobial and antifungal surface coatings with nanoparticles (silver, magnesium, zinc) • Lighter, stronger and more heat-resistant films with silicate nanoparticles • Modified permeation behavior of foils	• Nanosize powders to increase absorption of nutrients • Cellulose nanocrystal composites as drug carrier • Nanoencapsulation of neutraceuticals for better absorption, better stability or targeted delivery • Nanocochleates (coiled nanoparticles) to deliver nutrients more efficiently to cells without affecting color or taste of food • Vitamin sprays dispersing active molecules into nanodroplets for better absorption


APPLICATION OF NANOPARTICLES
Nanomedicine
Targeted drug delivery, Gene therapy, Cancer therapy, Photoimaging, Antioxidant activity, Antimicrobial activity, Mosquitocidal uses
Environment
Catalytic activity, Removal of toxic pollutant/ heavy metal/oil droplets/pesticides/insecticide / water remediation
Consumer goods & Electronics
Cosmetics, Fast moving consumer goods, Photonic crystals, Nonlinear opticals, Nanoelectronics, Labelling and Imaging
Agriculture
Gene delivery, Cell labelling, Nanocensors for biomolecules detection, Fertilizer delivery, Crop protection and production


Application of Nanotechnology in Food Industry
Food Processing
Food Packaging
ANTICAKING AGENT
Improve consistency & prevent lump formation
NANO ADDITIVES & NEUTRACEUTICALS
Improve nutritional value of food
GELATING AGENT
To improve of food texture
NANO CAPSULATION & NANOCARRIERS
To protect aroma, flavor and other ingredients in food
IMPROVED PACKAGING
Use of Nanoparticles to improved physical performance of food
ACTIVE PACKAGING
Nanoparticles as antimicrobial agent
SMART PACKAGING
Nano-biosensors for pathogen detection

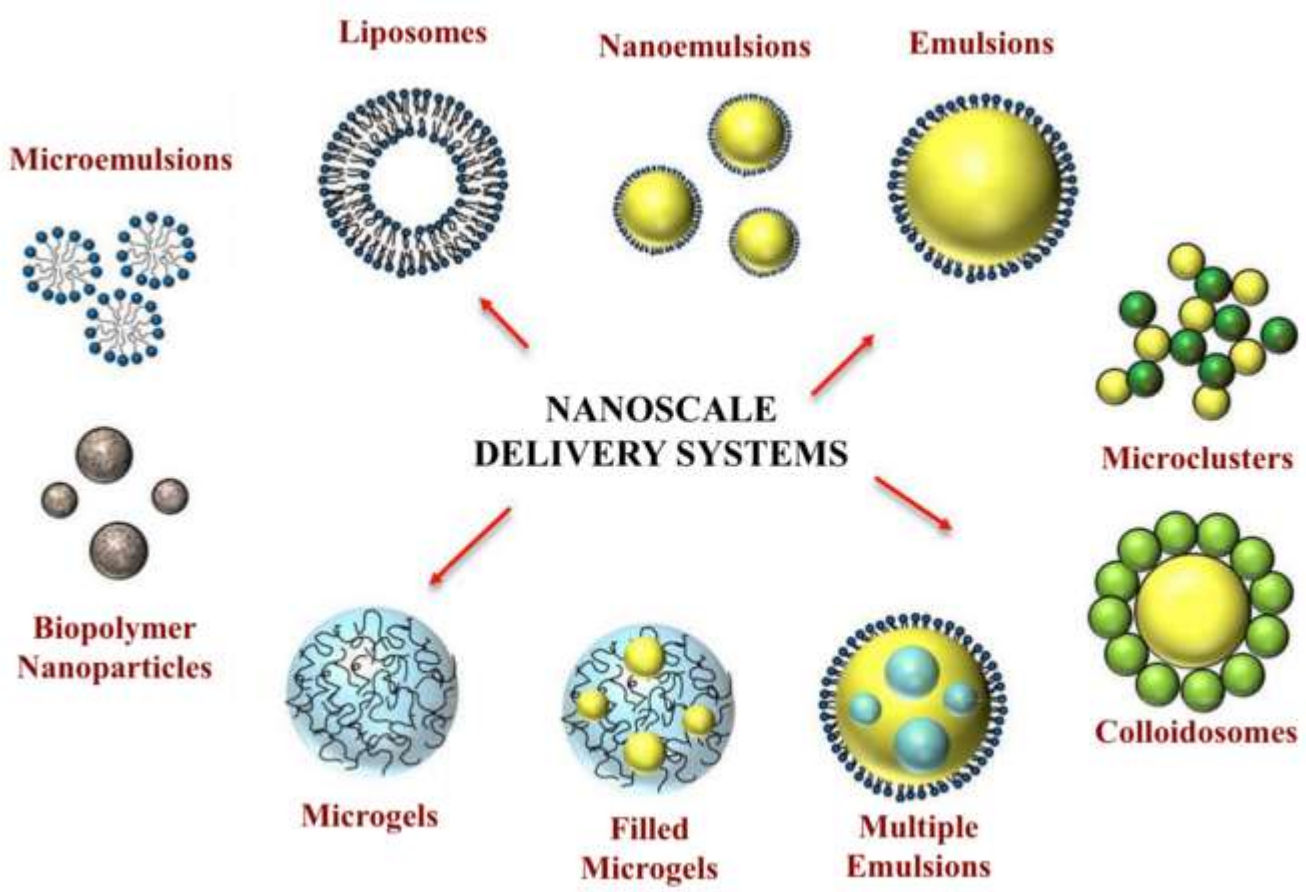
Nano and nutrition



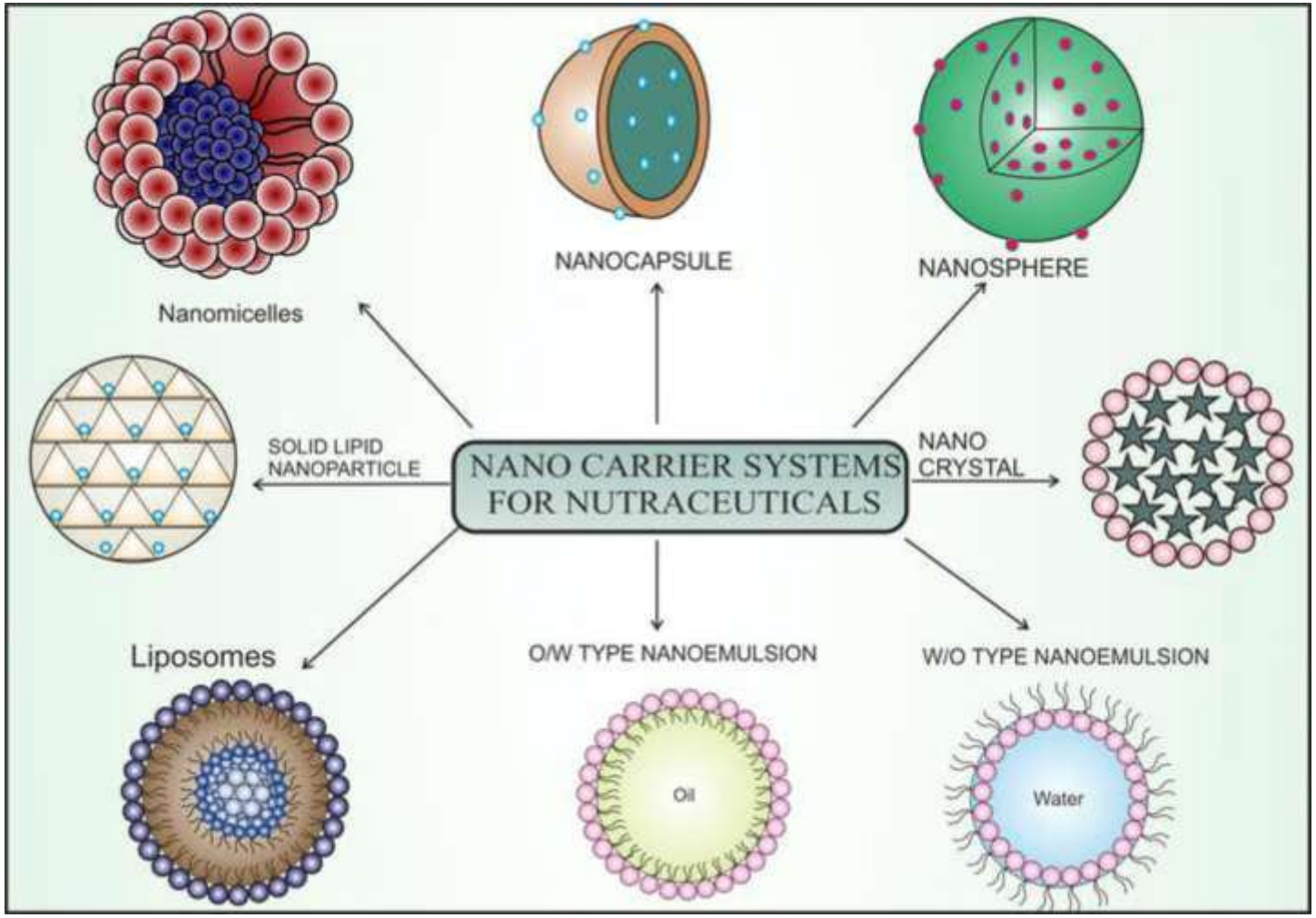
Methods Nano

Nanotechnique	Characteristic feature	Examples	Reference
Edible coatings	To preserve the quality of fresh foods during extended storage	Gelatin-based edible coatings containing cellulose nanocrystal	Fakhouri et al., 2014
		Chitosan/nanosilica coatings	Shi et al., 2013
		Chitosan film with nano-SiO_2	Yu et al., 2012
		Alginate/lysozyme nanolaminate coatings	Medeiros et al., 2014
Hydrogels	Can be easily placed into capsules, protects drugs from extreme environments, and to deliver them in response to environmental stimuli such as pH and temperature	Protein hydrogels	Qui and Park, 2001
Polymeric micelles	Solubilize water-insoluble compounds in the hydrophobic interior, high solubility, low toxicity	PEO-b-PCL [poly(ethylene glycol)block-poly(caprolactone)] polymeric micelles	Ma et al., 2008
		Methoxy poly(ethylene glycol) palmitate polymeric micelles	Sahu et al., 2008
Nanoemulsions	(i) Greater stability to droplet aggregation and gravitational separation;	β-Carotene-based nanoemulsion	Kong et al., 2011
	(ii) Higher optical clarity; and, (iii) increased oral bioavailability	β-Carotene-based nanoemulsion	Yuan et al., 2008
Liposomes	Since liposome surrounds an aqueous solution inside a hydrophobic membrane, it can be used delivery vehicles for hydrophobic molecules (contained within the bilayer) or hydrophilic molecules (contained in the aqueous interior)	Cationic lipid incorporated liposomes modified with an acid-labile polymer hyper-branched poly(glycidol) (HPG)	Yoshizaki et al., 2014
Inorganic NPs	They display good encapsulation capability and their rigid surfaces allow controlled functionalization	Mesoporous silica nanoparticles	Tang et al., 2012

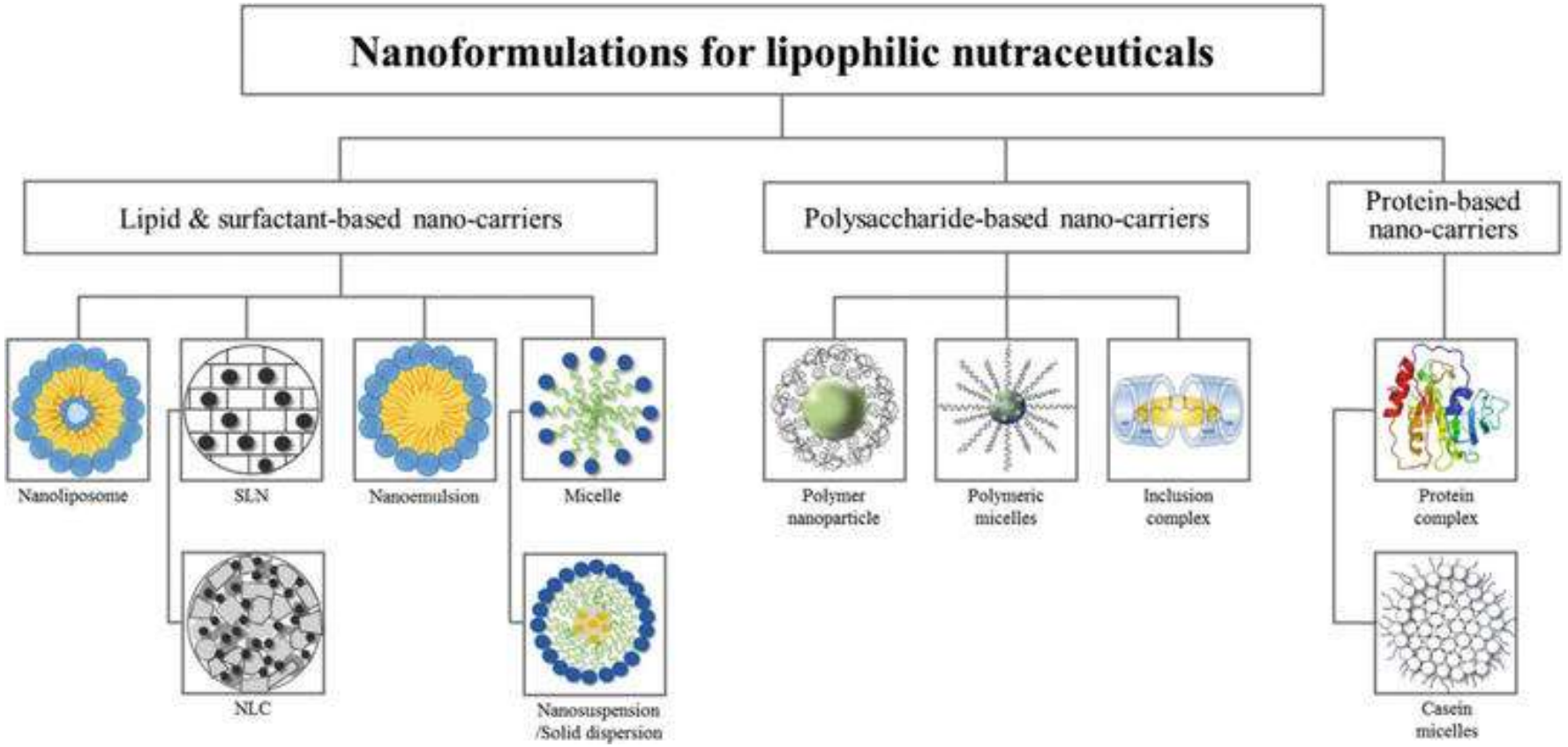
Nanoparticles: Delivery, stability, release



Nano carriers

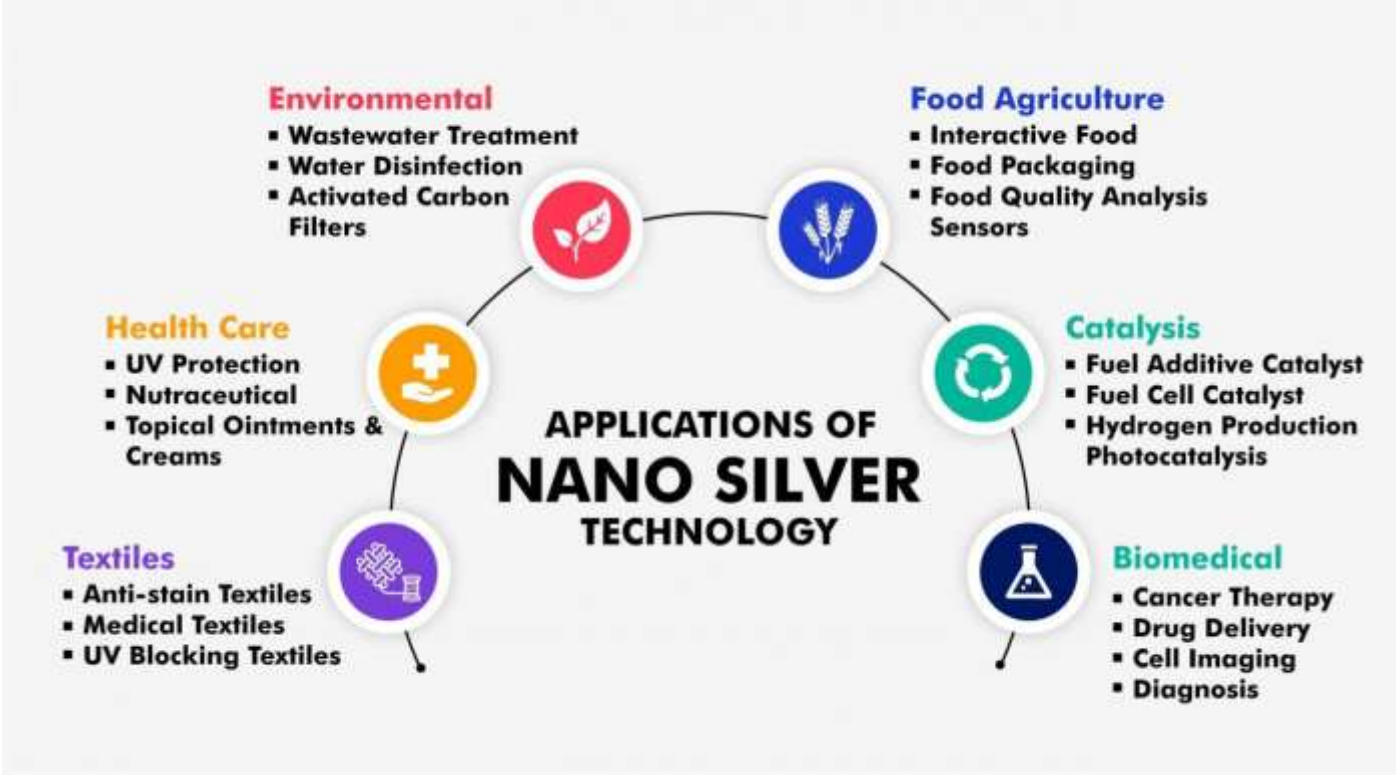


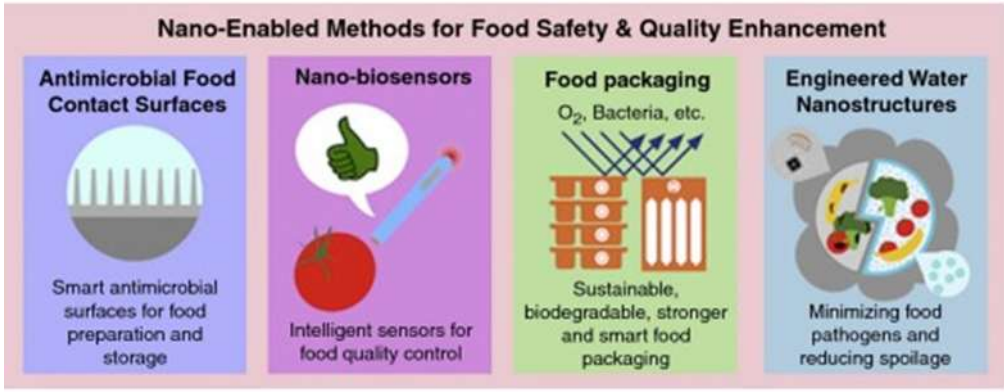
Nano and nutraceuticals

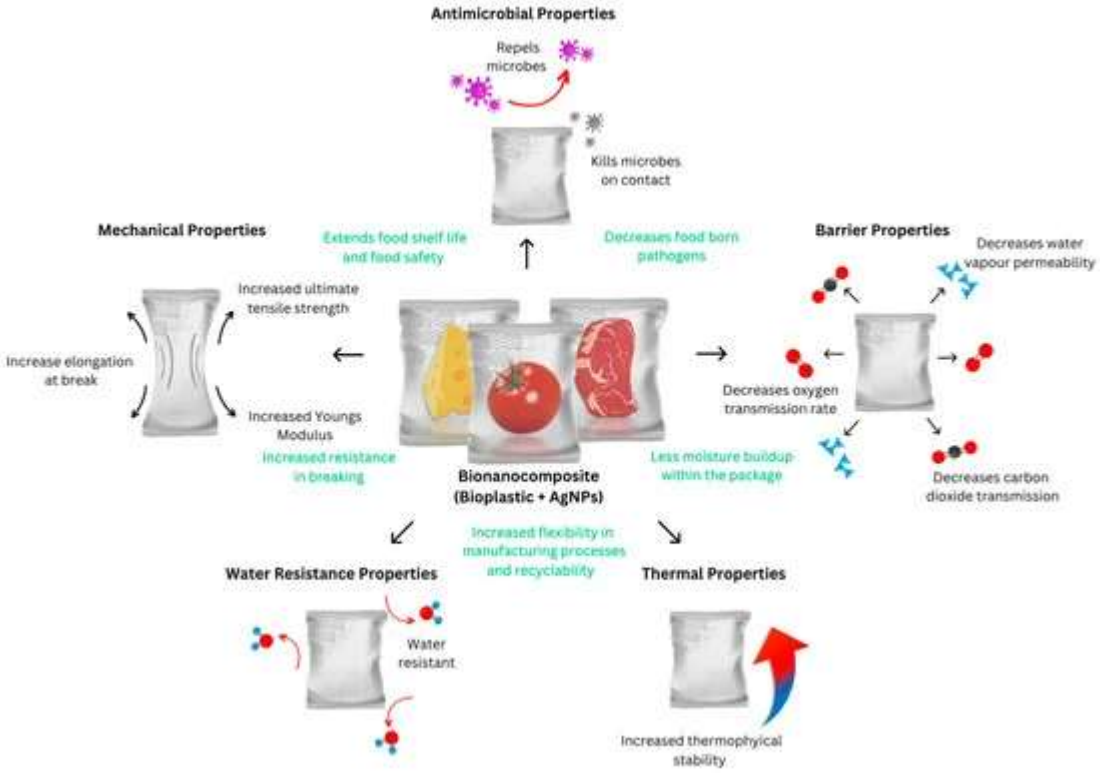



FutuNatura
60 capsules
LIPOSOMAL
CURCUMIN
With phospholipids
Increased bioavailability
FutuNatura
LIPOSOMAL
CURCUMIN
With phospholipids
Increased bioavailability
60 capsules
Food supplement

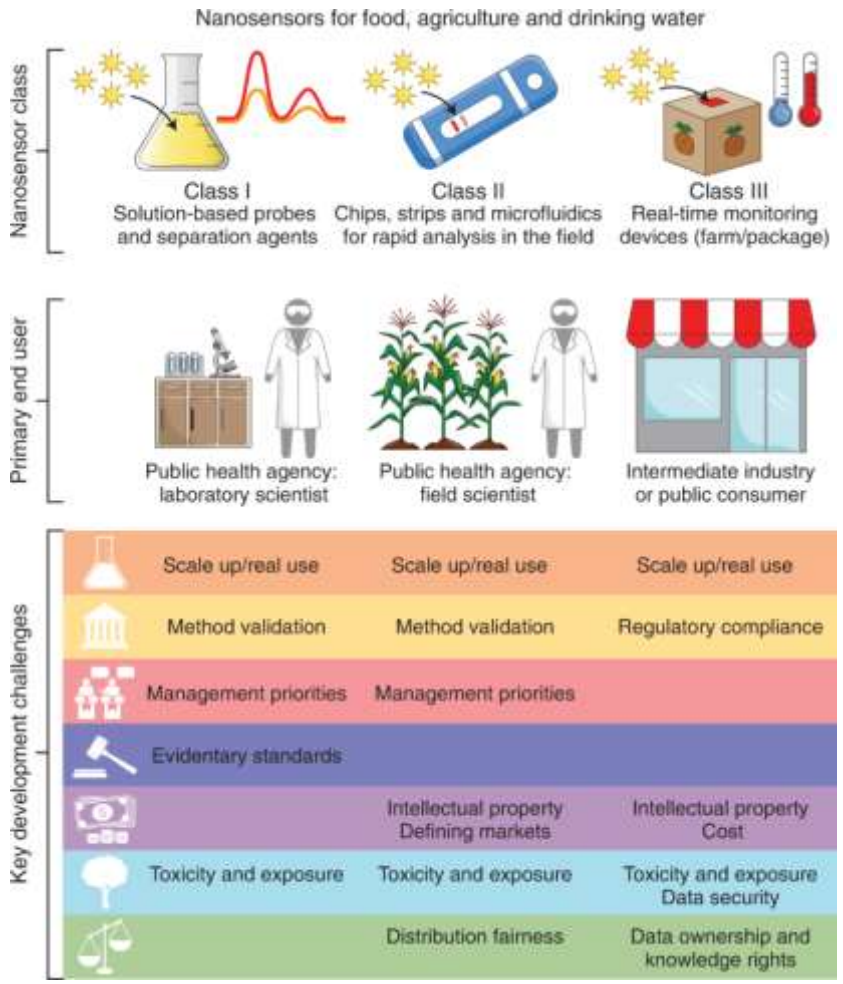
Nano silver


Environmental
▪ Wastewater Treatment
▪ Water Disinfection
▪ Activated Carbon Filters
Food Agriculture
▪ Interactive Food
▪ Food Packaging
▪ Food Quality Analysis Sensors
Health Care
▪ UV Protection
▪ Nutraceutical
▪ Topical Ointments & Creams
Catalysis
▪ Fuel Additive Catalyst
▪ Fuel Cell Catalyst
▪ Hydrogen Production Photocatalysis
APPLICATIONS OF
NANO SILVER
TECHNOLOGY
Textiles
▪ Anti-stain Textiles
▪ Medical Textiles
▪ UV Blocking Textiles
Biomedical
▪ Cancer Therapy
▪ Drug Delivery
▪ Cell Imaging
▪ Diagnosis

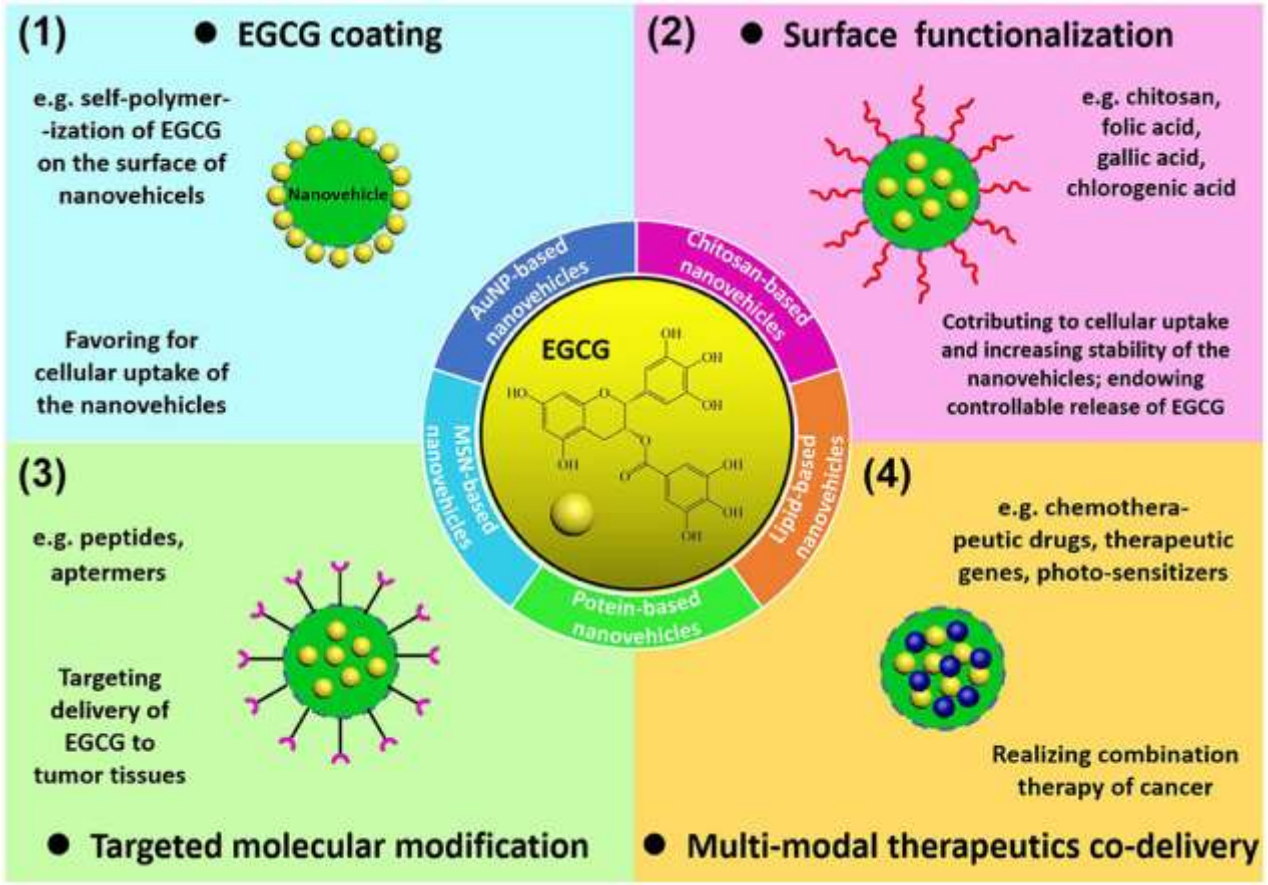

Nano-Enabled Methods for Food Safety & Quality Enhancement
Antimicrobial Food Contact Surfaces
Smart antimicrobial surfaces for food preparation and storage
Nano-biosensors
Intelligent sensors for food quality control
Food packaging
O_2, Bacteria, etc.
Sustainable, biodegradable, stronger and smart food packaging
Engineered Water Nanostructures
Minimizing food pathogens and reducing spoilage

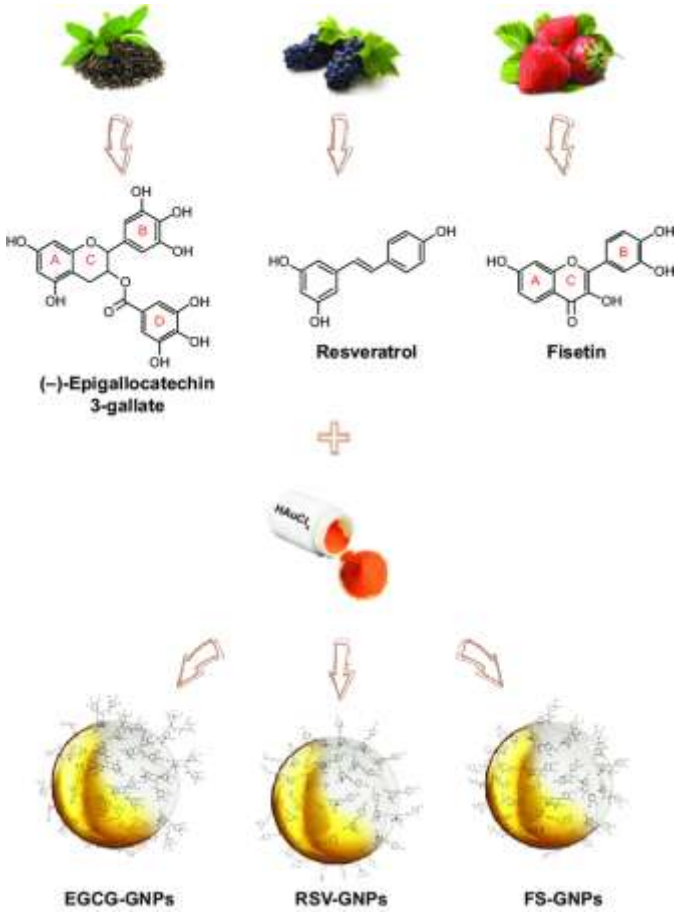

Antimicrobial Properties
Repels microbes
Kills microbes on contact
Mechanical Properties
Extends food shelf life and food safety
Decreases food born pathogens
Barrier Properties
Decreases water vapour permeability
Increased ultimate tensile strength
Increase elongation at break
Increased Youngs Modulus
Increased resistance in breaking
Bionanocomposite (Bioplastic + AgNPs)
Less moisture buildup within the package
Decreases oxygen transmission rate
Decreases carbon dioxide transmission
Increased flexibility in manufacturing processes and recyclability
Water Resistance Properties
Water resistant
Thermal Properties
Increased thermophyical stability

Nano sensors

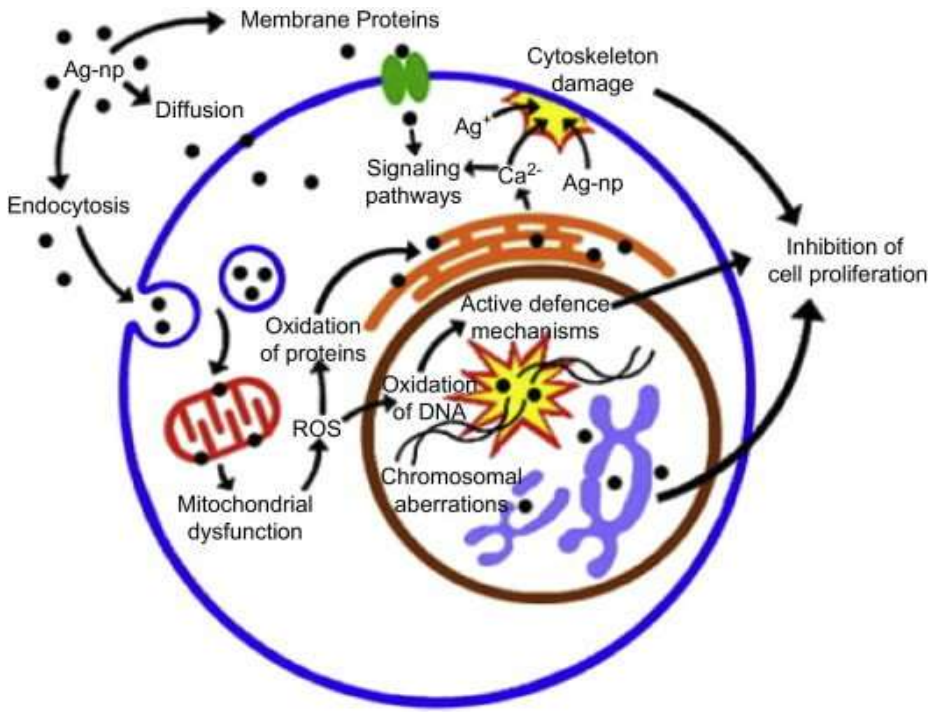


Nutraceuticals delivery





Gold nanoparticles , GNPs

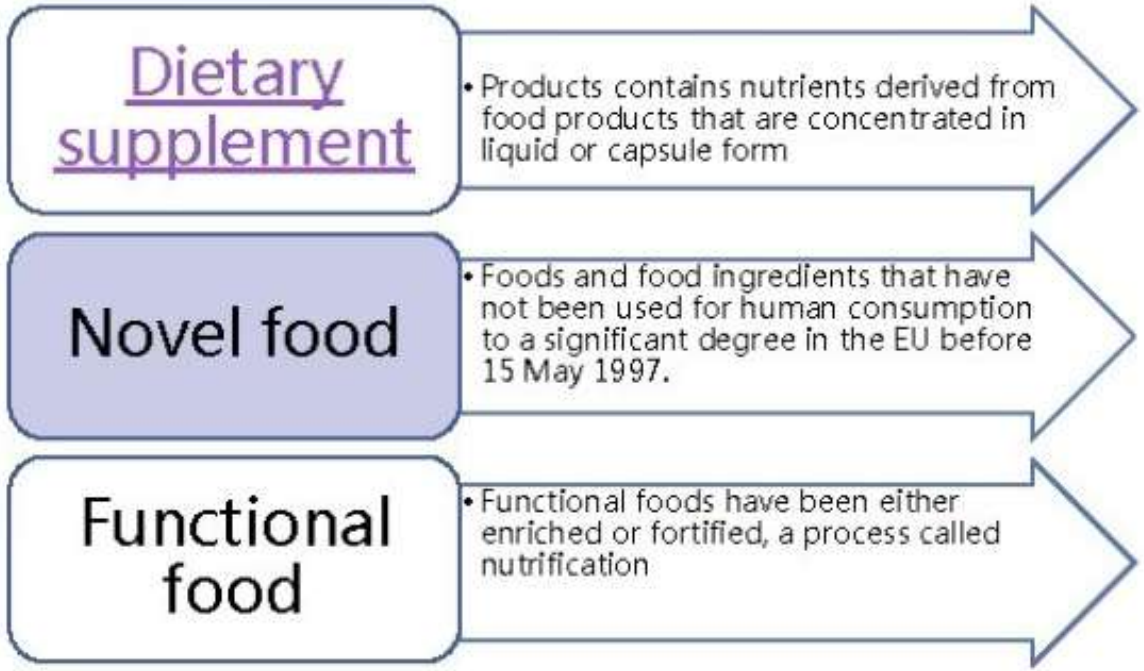


In general, in vitro studies have shown adverse health effects of cells or bacteria after exposure to AgNPs. The mechanism of AgNP-dependent cytotoxicity in in vitro assays is primarily based on the induction of reactive oxygen species (ROS). Cytotoxicity and genotoxicity of AgNPs depend mainly on the size, concentration, and duration of exposure. Exposure to silver nanoparticles causes a decrease in GSH levels (glutathione), lipid peroxidation, increased expression of ROS-responsive genes, and an increased level of their proteins, which in turn leads to DNA damage, apoptosis, and necrosis [25].

In general, in vitro studies have shown adverse health effects of cells or bacteria after exposure to AgNPs. The mechanism of AgNP-dependent cytotoxicity in in vitro assays is primarily based on the induction of reactive oxygen species (ROS). Cytotoxicity and genotoxicity of AgNPs depend mainly on the size, concentration, and duration of exposure. Exposure to silver nanoparticles causes a decrease in GSH levels (glutathione), lipid peroxidation, increased expression of ROS-responsive genes, and an increased level of their proteins, which in turn leads to DNA damage, apoptosis, and necrosis [25].

Supplements, NF, functional foods

EFSA



efsa
European Food Safety Authority

Nutraceuticals, Botanicals

Foods for special medical purposes

Supplements,Food improvements

Food

FOOD IMPROVEMENT AGENTS

- Additives
- Enzymes
- Flavourings
- Extraction Solvents
- Common Authorisation Procedure

ALL TOPICS

Food Improvement Agents

Food additives, food enzymes and food flavourings are also known as "food improvement agents".

Why add food additives, enzymes and flavourings to food?

- Among others, food additives preserve, colour and stabilise food during its production, packaging or storage.
- Enzymes have specific biochemical actions which serve technological purposes at any stage of the food chain
- Flavourings give or change the odour or taste to food

Safe level

Setting the “safe level”
As part of its safety evaluations of food additives EFSA seeks to establish, when possible (e.g. when sufficient information is available), an Acceptable Daily *Intake* (*ADI*) for each substance.

The ADI is the amount of a substance that people can consume on a daily basis during their whole life without any appreciable health risk. ADIs are usually expressed in mg per kg of body weight per day (mg/kg bw/day). The ADI can apply to a specific additive or a group of additives with similar properties. When re-evaluating previously authorised additives, EFSA may either confirm or amend an existing ADI following review of all available evidence.
When there are insufficient data for establishing an ADI, a *margin of safety* may be calculated to determine whether estimated *exposure* might be of potential concern.
In other cases, for example, for substances that are already present in the body or regular components of the diet or that did not indicate adverse effects in animal studies, there is no need to set an ADI.

Supplements , EU upper intake levels

Food supplements

8 minutes read

Share:

Contents

Latest
Milestones
EFSA's role
EU framework
FAQ
Published on this
See also

Food supplements are concentrated sources of nutrients (i.e. *mineral* and vitamins) or other substances with a nutritional or physiological effect that are marketed in "*dose* " form (e.g. pills, tablets, capsules, liquids in measured doses). A wide range of nutrients and other ingredients might be present in food supplements, including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fibre and various plants and herbal extracts.

Food supplements are intended to correct nutritional deficiencies, maintain an *adequate intake* of certain nutrients, or to support specific physiological functions. They are not medicinal products and as such cannot exert a pharmacological, immunological or metabolic action. Therefore their use is not intended to treat or prevent diseases in humans or to modify physiological functions.

In the EU, food supplements are regulated as foods. Harmonised legislation regulates the vitamins and minerals, and the substances used as their sources, which can be used in the manufacturing of food supplements. For ingredients other than vitamins and minerals, the European Commission has established harmonised rules to protect consumers against potential health risks and maintains a list of substances which are known or suspected to have adverse effects on health and the use of which is therefore controlled.

Latest

In May 2018, the EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS) adopted guidance on the evaluation of sources of nutrients and *bioavailability* of nutrient from the sources.

In December 2017, EFSA published the Summary report on Dietary Reference Values for nutrients. Earlier in 2017, EFSA published the Overview on Tolerable Upper Intake Levels as derived by the Scientific Committee on Food (SCF) and the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA).

Supplements Intake levels

Table 2: Summary of Tolerable Upper Intake Levels (UL) of **vitamins and certain fatty acids**

	Unit	Age/Life-stage group								
		0-6 mo	6-12 mo	1-3 y	4-6 y	7-10 y	11-14 y	15-17 y	Adults	Pregnancy	Lactation
VITAMINS											
Biotin		No adequate data to derive a UL									
β-Carotene		No adequate data to derive a UL									
Folic acid (synthetic)	µg/d			200	300	400	600	800	1000	1000	1000
Niacin											
Nicotinamide	mg/d			150	220	350	500	700	900	Inadequate data	
Nicotinic acid	mg/d			2	3	4	6	8	10	Inadequate data	
Pantothenic acid		No adequate data to derive a UL									
Vitamin A[a]	µg RE/d			800	1100	1500	2000	2600	3000[b]	3000	3000
Vitamin B1		No adequate data to derive a UL									
Vitamin B12		No clearly defined adverse effects									
Vitamin B2		No adequate data to derive a UL									
Vitamin B6	mg/d			5	7	10	15	20	25	25	25
Vitamin C		No adequate data to derive a UL									
Vitamin D	µg/d	25	35	50	50	50	100	100	100	100	100
Vitamin E	mg/d			100	120	160	220	260	300	300	300
Vitamin K		No adequate data to derive a UL									
FATTY ACIDS											
DHA, EPA, DPA		No adequate data to derive a UL									

d, day; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; mo, month; RE, retinol equivalents; y, year

Botanicals EU

Foods for special medical purposes

European Food Safety Authority EFSA Journal 2015;13(11):4300

SCIENTIFIC OPINION

Scientific and technical guidance on foods for special medical purposes in the context of Article 3 of Regulation (EU) No 609/2013[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA) was asked to provide scientific and technical guidance on foods for special medical purposes in the context of Article 3 of Regulation (EU) No 609/2013. The guidance presented in this document is to assist in the preparation and presentation of well-structured dossiers. It presents a common format for the organisation of the information and outlines the information and scientific data which could be included in the dossier, as well as the key issues which should be addressed in the dossier in order to assess the extent to which a food product notified as FSMP falls under the scope of Regulation (EU) No 609/2013, under the proposed use. It is intended that the guidance will be kept under review and will be further amended and updated as appropriate in the light of experience gained from the evaluation of dossiers for specific food products notified as FSMP, and in the light of future Community guidelines and legislation. The scope of this guidance is limited to FSMPs in the context of Article 3 of Regulation (EU) No 609/2013. Out of the scope of this guidance are: a) other categories of food falling under Regulation (EU) No 609/2013, such as infant formula and follow-on formula, processed cereal-based food and baby food, and total diet replacement for weight control; b) meal replacements for weight control; c) "gluten-free" and "lactose-free" foods.

Scientific and technical guidance on foods for special medical purposes in the context of Article 3 of Regulation (EU) No 609/2013

Published: 26 March 2021

Share:

Wiley Online Library

Full article:

Read online at EFSA Journal | Full article (online viewer)

Meta data

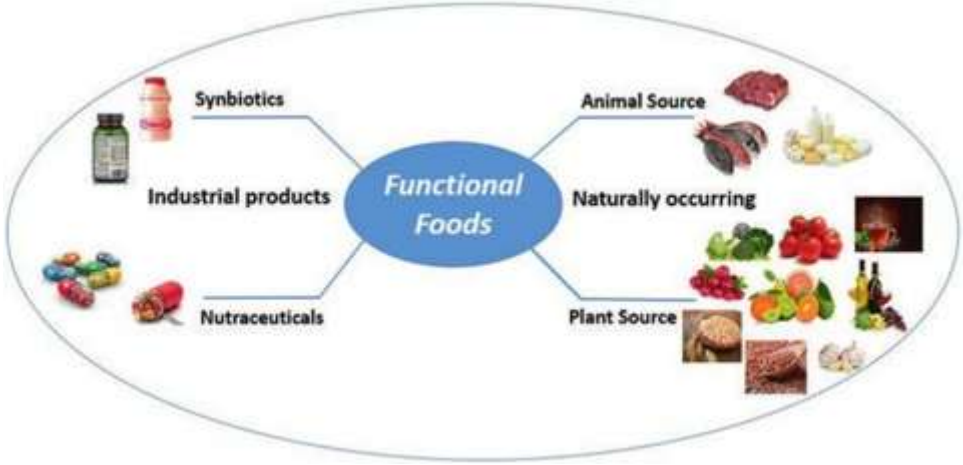
EFSA Journal 2021;19(3):6544

DOI https://doi.org/10.2903/j.efsa.2021.6544

KEYWORDS food product, disease, disorder, medical condition, patients, dietary management

Functional foods (non specifically regulated in EU)

- Functional foods are defined as “any food and food ingredients that may provide health benefit beyond the traditional nutrition that it contains”.
- **Japan** was the first country to recognize functional foods as a separate category when in **1991** it introduced the **FOSHU (Foods for Specific Health Use)** system to evaluate health claims.
- FSSAI issues Gazette notification for regulations on Nutraceuticals, Functional Foods, Novel Foods and others on 23 December 2016.



Nutraceuticals, Botanicals , EU

European Food Safety Authority

EFSA Journal 2012;10(5):2663

SCIENTIFIC REPORT OF EFSA

Compendium of botanicals reported to contain naturally occuring substances of possible concern for human health when used in food and food supplements[1]

European Food Safety Authority[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

In April 2009, EFSA published on its website a Compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances of concern. The purpose of the Compendium is to assist risk assessors responsible for the evaluation of specific ingredients in food supplements, in more easily identifying the compound(s) of concern on which to focus the assessment. The Scientific Committee worked on a second version of that Compendium between January 2010 and February 2012, considering botanicals that appear on a negative list or subject to restricted use (e.g. max. level or certain parts allowed only) in at least one European Member State. Two annexes have been added compared to the first version; the first one lists botanicals for which not enough information on possible substances of concern could be found, or for which the information present could not be verified. The second one lists botanicals for which, although some data were available, the Scientific Committee could not identify substances of concern, or other reasons for the inclusion in the compendium. This new "Compendium of botanicals reported to contain naturally occuring substances of possible concern for human health" replaces the first version published in 2009; it lists in alphabetical order botanicals without any judgment on whether they are suitable or not suitable for food applications in Europe; it has no legal or regulatory force pertaining to the legal classification of products or substances.

Example, botanical

EFSA/SC/COMP/445rev45

COMPENDIUM OF BOTANICALS REPORTED TO CONTAIN NATURALLY OCCURING SUBSTANCES OF POSSIBLE CONCERN FOR HUMAN HEALTH WHEN USED IN FOOD AND FOOD SUPPLEMENTS

This compendium lists in alphabetical order botanicals without any judgment on whether these are suitable or not suitable for food applications in Europe. This compendium is part of a preliminary work undertaken by EFSA to harmonise the methodology across its panels for assessing the s botanicals and botanical preparations used in food and food supplements. Without prejudice to the existing legal framework, such compendium has no legal status and may not be used as support or evidence in any disagreement or dispute pertaining to the legal classification of products or substanc compendium is a living document and is therefore open for additional contributions and comments.

Botanical name	Family	parts of plants of possible concern	Chemical of concern	Remarks on toxic/adverse effect(s) not known to be related to the identified chemical(s) of concern	Specific References
***Cucumis sativus* L.**	Cucurbitaceae	Whole plant	Possible occurence of the oxygenated tetracyclic triterpenes: cucurbitacin C in leaf and fruit and of cucurbitacins C and B in root.		Van Keulen HA. 1981. Fluorodensitometric estimation of cucurbitacin-C in leav Cucumis sativus L.. Plant Foods for Human Nutrition (Formerly Qualitas Plantz 31(2), 129-137.
***Cucurbita maxima* Duch.**	Cucurbitaceae	Whole plant	Possible occurrence of oxygenated tetracyclic triterpenes: cucurbitacins B and C.		Rehm S.et al. 1957. Bitter principles of the cucurbitaceae. VIII.—cucurbitacins seedlings—occurrence, biochemistry and genetical aspects. J. Sci. Food. Agr. 8(12), 687 - 691
***Cucurbita pepo* L.**	Cucurbitaceae	Fruit	Possible occurrence of oxygenated tetracyclic triterpenes: cucurbitacins.	Fruits of cultivated squash and other pumpkins have been cultured to be "free of cucurbitacins", and are assumed to contain a supressor gene or a mutation responsible for absence of cucurbitacins. However, back-mutations occur randomly which may lead to plants with toxic and bitter fruits.	Tema Nord 2006:556, Cucurbitacins in plant food, Nordic Council of Ministers. 893-1381-1
***Cuminum cyminum* L.**	Apiaceae (Umbelliferae)	Fruit	Essential oil from fruit: phenylpropanoids: e.g. methylchavicol (30ppm) and monoterpenes: monoterpene etheroxide: 1,8-cineole (0.2-0.4%).		Council of Europe. 2007. Natural sources of flavourings. Report No. 2. Counci Europe Publishing. ISBN 978-92-871-6156-7.
***Curcuma kwangsiensis* S.G.Lee & C.F. Liang**	Zingiberaceae	Rhizome	Essential oil: monoterpene etheroxide: 1,8-cineole.		Zhu You-Ping. 1998. Chinese Materia medica. Chemistry, pharmacology and applications. CRC Press. ISBN-13: 978-9057022852
***Curcuma longa* L.** (*Curcuma domestica* Val., *Curcuma domestic* Loir., *Amomum curcuma* Jacq.)	Zingiberaceae	Rhizome	Essential oil: monoterpene etheroxide: 1,8-cineole and bicyclic monoterpenes: e.g. camphor		Council of Europe. 2000. Natural sources of flavourings. Report No. 1. Counci Europe Publishing. ISBN 978-92-871-4324-2. Zhu You-Ping. 1998. Chinese Materia medica. Chemistry, pharmacology and applications. CRC Press. ISBN-13: 978-9057022852
***Curcuma phaeocaulis* Valeton**	Zingiberaceae	Rhizome	Essential oil: bicyclic monoterpenes: e.g. camphor (10-16%)		Zhu You-Ping. 1998. Chinese Materia medica. Chemistry, pharmacology and applications. CRC Press. ISBN-13: 978-9057022852
***Curcuma wenyujin* Y.H.Chen & C.Ling**	Zingiberaceae	Rhizome			Zhu You-Ping. 1998. Chinese Materia medica. Chemistry, pharmacology and applications. CRC Press. ISBN-13: 978-9057022852. Li S. et al. 2011. Chemical Composition and Product Quality Control of Turme (Curcuma longa L.) Pharmaceutical Crops, 2: 28-54
***Curcuma xanthorrhiza* Roxb.**	Zingiberaceae	Rhizome	Essential oil (3-12%): monoterpenes: monoterpene etheroxide: 1,8-cineole (up to 40%), bicyclic monoterpenes: camphor (1%);		Bruneton J. 2009. Pharmacognosie. (Phytochimie, Plantes médicinales), Ed. T Lavoisier, Paris. 4ème édition, 1269 pages, ISBN : 978-2-7430-1188-8; Hagei Handbuch der Pharmazeutischen Praxis 1998. Springer Verlag. ISBN 3-540-5
***Cyathula officinalis* Kuan**	Amaranthaceae (Chenopodiaceae)	Root	Coumarins: e.g. scoparone (6,7 dimethoxycoumarin)	The saponins (hederagenin- and gypsogmin -type saponins) are thought to stimulate uterus contraction and can lead to abortion, however scoparone is probably the causative agent.	Chandhoke N. 1979. Scoparone: effect on reproductive processes in rats. Indi Biol. 17, 740-742. Ren MT et al. 2009. Rapid analysis of constituents of Radix Cyathulae using hy interaction-reverse phase LC-MS. Journal of Separation Science. 32(22), 398 Zhu You-Ping. 1998. Chinese Materia medica. Chemistry, pharmacology and applications. CRC Press. ISBN-13: 978-9057022852
***Cycas* spp.**	Cycadaceae	Leaf, pollen, seed	Genus in which species may contain the amine oxide: cycasin		Eizirik DL and Kisby GE. 1995. Cycad toxin-induced damage of rodent and hu pancreatic beta-cells. Biochem. Pharmacol. 50(3), 355-365. Salama M and Arias-Carrión O . 2011. Natural toxins implicated in the develop Parkinson's disease. Therapeutic Advances in Neurological Disorders. 4(6), 3

Example EGCG

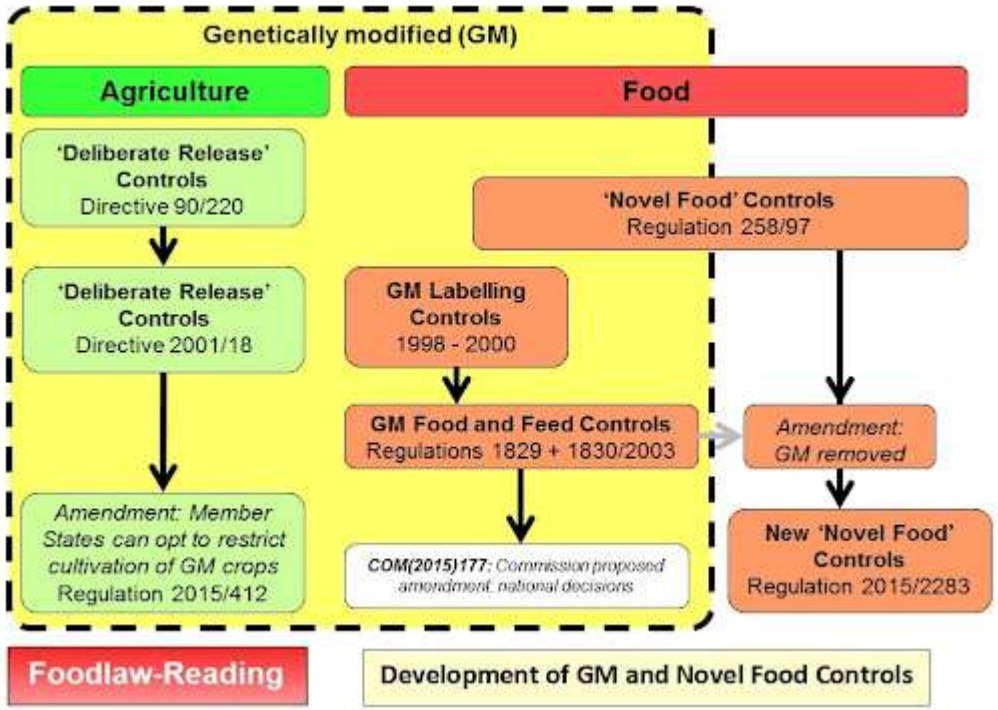
Green tea is produced from the leaves of *Camellia sinensis* (L.) Kuntze, without fermentation, which prevents the oxidation of polyphenolic components. Most of the polyphenols in green tea are catechins.
The Panel considered the possible association between the consumption of (-)-epigallocatechin-3-gallate (EGCG), the most relevant catechin in green tea, and hepatotoxicity. This scientific opinion is based on published scientific literature, including interventional studies, monographs and reports by national and international authorities and data received following a public 'Call for data'.
The mean daily intake of EGCG resulting from the consumption of green tea infusions ranges from 90 to 300 mg/day while exposure by high-level consumers is estimated to be up to 866 mg EGCG/day, in the adult population in the EU. Food supplements containing green tea catechins provide a daily dose of EGCG in the range of 5–1,000 mg/day, for adult population. The Panel concluded that catechins from green tea infusion, prepared in a traditional way, and reconstituted drinks with an equivalent composition to traditional green tea infusions, are in general considered to be safe according to the presumption of safety approach provided the intake corresponds to reported intakes in European Member States. However, rare cases of liver injury have been reported after consumption of green tea infusions, most probably due to an idiosyncratic reaction. Based on the available data on the potential adverse effects of green tea catechins on the liver, the Panel concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG/day taken as a food supplement has been shown to induce a statistically significant increase of serum transaminases in treated subjects compared to control.

New EU legislation restricts the amount of green tea extract containing (-)-epigallocatechin-3-gallate (EGCG) that can be present in food and sets new labeling requirements. EGCG is a catechin, which are flavinols that may lead to liver damage.

Catechins, of which EGCG is the most common type, are found naturally in the leaves of *Camellia sinensis* (L.) Kuntze, the plant that is processed into green tea. A 2018 scientific opinion from the European Food Safety Authority (EFSA) concluded that consumption of EGCG exceeding 800 milligrams per day (mg/day) may increase the likelihood of liver damage when taken as a food supplement. EFSA's determination was based on studies that revealed a statistically significant increase of serum transaminases, which are indicative of liver injury, in subjects given EGCG supplements.

Food supplements containing green tea atechins provide a daily dose of EGCG in the range of 5–1,000 mg/day, according to EFSA.

Developments novel food regulation, vertical, horizontal



Novel Food (EU)

Novel food

- Foods and food ingredients
  - with a new or intentionally modified primary molecular structure (eg, fat substitutes);
  - consisting of microorganisms, fungi or algae, or can be isolated from this (for example, microalgae oil);
  - consisting of plants or isolated (eg phytosterols), and isolated from animals food ingredients.

NF categories

1. Food with a new or intentionally modified molecular structure;
2. Food consisting of, isolated from or produced from microorganisms, fungi or algae;
3. Food consisting of, isolated from or produced from material of mineral origin;
4. Food consisting of, isolated from or produced from plants or their parts;
5. Food consisting of, isolated from or produced from animals or their parts;
6. Food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae;
7. Food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances;
8. Food consisting of engineered nanomaterials;
9. Vitamins, minerals and other substances used in accordance with Directive 2002/46/EC, Regulation (EC) No 1925/2006 or Regulation (EU) No 609/2013;
10. Food used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements as defined in point (a) of Article 2 of Directive 2002/46/EC;

e.g.
wild plants can be novel foods if they have not been consumed for human consumption to a significant degree in the EU before 15 May 1997

Novel foods

What are novel foods?

Novel foods are all foods that have not been used for human consumption to a significant degree within the European Union before 15 May 1997, irrespective of the dates of accession of Member States to the Union, and fall into at least one of the following 10 food categories:

1.with a new or intentionally modified molecular structure (e.g. tagatose, salatrim)
2.consist of or are isolated from microorganisms, fungi or algae (e.g. algae oil from the microalgae *Ulkenia sp*.)
3.consist of or are isolated from materials of mineral origin (e.g. clinoptilolite (zeolite))
4.consist of or are isolated from plants and parts of plants (e.g. noni juice (*Morinda citrifolia*), chia seeds*(Salvia hispanica*))
5.consist of or have been isolated from animals or their parts (e.g. insects, oil from Antarctic krill*(Euphasia superba)* , peptides from the fish *Sardinops sagax*)
6.cell and tissue cultures from animals, plants, microorganisms, fungi or algae (e.g. extract from cell cultures of *Echinacea angustifolia*, in vitro meat)
7.food resulting from a production process not used for food production within the Union before 15 May 1997 resulting in a change in composition or structure (e.g. high pressure pasteurised fruit preparations, UV-treated mushrooms*(Agaricus bisporus*), UV-treated baker's yeast*(Saccharomyces cerevisiae*), UV-treated milk)
8.consist of engineered nanomaterials (according to Article 3, Para. 2, lit f)
9.vitamins, minerals and other substances (e.g. iron (II) ammonium phosphate, vitamin K2 (menaquinone), chromium picolinate)
10.used exclusively in food supplements (not permitted in food categories other than food supplements) (e.g. maqui berry (*Aristotelia chilensis*), rose root*(Rhodiola rosea*)

Novel foods

The Commission considers foods and food ingredients that have not been used for human consumption to a significant degree in the EU before 15 May 1997 novel foods and novel food ingredients.

Applies to foods and food ingredients which satisfy the decription and fall into one of the following categories:
Foods and food ingredients

- which present a new or modified primary molecular structure;
- which consist of micro-organisms, fungi or algae;
- which consist of or are isolated from plants and ingredients isolated from animals;
- whose nutritional value, metabolism or level of undesirable substances has been significantly changed by the production process.

They:
Must be safe for consumers.
Must be properly labelled to not mislead consumers.
Can not be nutritionally disadvantageous.

What the Novel Food Regulation does not cover
The Regulation does not cover :

- Food additives
- Flavourings for use in foods
- Extraction solvents used in the production of foods
- GMOs for food and feed

If foods and/or food ingredients were used exclusively in food supplements, new uses in other foods require authorisation under the Novel Food Regulation e.g. food fortification require authorisation.

On the market before 15 May 1997, consequences

VESIsorb® Drug Delivery System

VESIsorb® has made positive impacts in multiple markets, taking absorption and bioavailability to new levels that dramatically exceed industry standards. This allows for an unmatched range of product applications and novel formulations. It has successfully been applied to the most popular, science-backed ingredients like omega-3 EFAs, coenzyme Q10, QH ubiquinol, vitamin K2, curcumin, phytocannabinoids, vitamin D, pterostilbene, palm tocotrienols, diindolylmethane (DIM), gamma tocopherols, citrus polymethoxylated flavones (PMFs), resveratrol, krill oil, algal DHA, vitamin A (retinoids), phospholipids and beta-caryophyllene, among many others.

"Natural products utilizing VESIsorb® have historically set the benchmark for delivering superior absorption and blood plasma levels that allow the body to use more of the active ingredients. This provides confidence that health conscious consumers will receive the maximum benefits from the key ingredients found in our products." *- Dr. Barry Ritz, Nestlé Health Science*

Questions of interpretation on the Novel Food Regulation - Topic Spermidine

20. June 2022 | *by* Jakob Hütthaler-Brandauer *in* Life Sciences

Reference for a preliminary ruling from the LG Graz, Case C-141/22 - Questions of interpretation concerning the Novel Food Regulation / Subject: Spermidine

The method relates to a food supplement comprising **Spermidine**, in which buckwheat seed germinates into sprouts a hydroponics in a nutrient solution containing synthetic spermidine. After harvesting, the seedling is washed with wate dried and ground into seedling meal. The production process does not produce more sprouts than seedlings are used. The spermidine content of buckwheat seedling flour is 3.5 mg per gram.

The court referred the following questions to the ECJ:

1) Is Article 3(2)(a)(iv) of Regulation (EU) 2015/2283 to be interpreted as meaning that "high spermidine buckwheat seedling flour" constitutes a novel food, provided that only buckwheat seedling flour with a non-increased spermidine content has been used to a significant extent for human consumption in the European Union before 15 May 1997 or has a history of use as a safe food thereafter, irrespective of how the spermidine enters the buckwheat seedling flour?

2) If the answer to Question 1 is in the negative, is Article 3(2)(a)(vii) of Regulation 2015/2283 to be interpreted as meaning that the term 'food manufacturing process' also includes processes in primary production?

3) If the answer to Question 2 is in the affirmative, does the question of the novelty of a manufacturing process within the meaning of Article 3(2)(a)(vii) of Regulation 2015/2283 depend on whether the manufacturing process itself has

Do novel foods have to be safe?

Novel foods must be subject to a uniform safety assessment before they can be placed on the market in the EU. Novel foods must not pose a risk to the consumer and must not be misleading. Furthermore, they must not differ from the conventional foods and food ingredients they are intended to replace in such a way that their normal consumption would result in nutritional deficiencies for the consumer.

What is not covered by the Novel Food Regulation?

Food additives, food flavourings, food enzymes, genetically modified food and extraction solvents for the production of food are not novel foods, as they are subject to their own legal regulations (according to Article 2, para. 2).

Clarification of Novel Food Status

The food business operator is responsible for verifying whether the food to be placed on the market is a novel food. To clarify the Novel Food status, it is recommended to consult the Union list (Implementing Regulation (EU) 2017/2470 as amended consolidated version) as well as the Novel Food Catalogue of the European Commission. The Novel Food Catalogue of the European Commission provides information on the Novel Food status of foods and ingredients. Since 01 January 2018 there is the Union list, a positive list in which all approved Novel Foods are listed. If a Novel Food is already listed in the Union list, it can be placed on the market under compliance with the conditions of use and specifications. Another aid for clarifying the Novel Food status are the German Substance Lists, which are intended to provide an overview of the use of plants and fungi in foodstuffs.

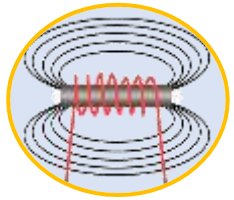
For determining the criterion "significant consumption before 15 May 1997", the guideline "human consumption to a significant degree" published by the European Commission is used.

In case of existing uncertainty as to whether the food is an unauthorised novel food, the food business operator may consult the competent authority of the Member State in which the potentially novel food is to be placed on the market first (= Consultation procedure according to Article 4 of Novel Food Regulation (EU) 2015/2283).

Novel foods because of processing technologies

Novel Food Processing Technologies

Thermal



Electro-magnetic

Biotechnological

Mechanical

Combination

Ensure food safety

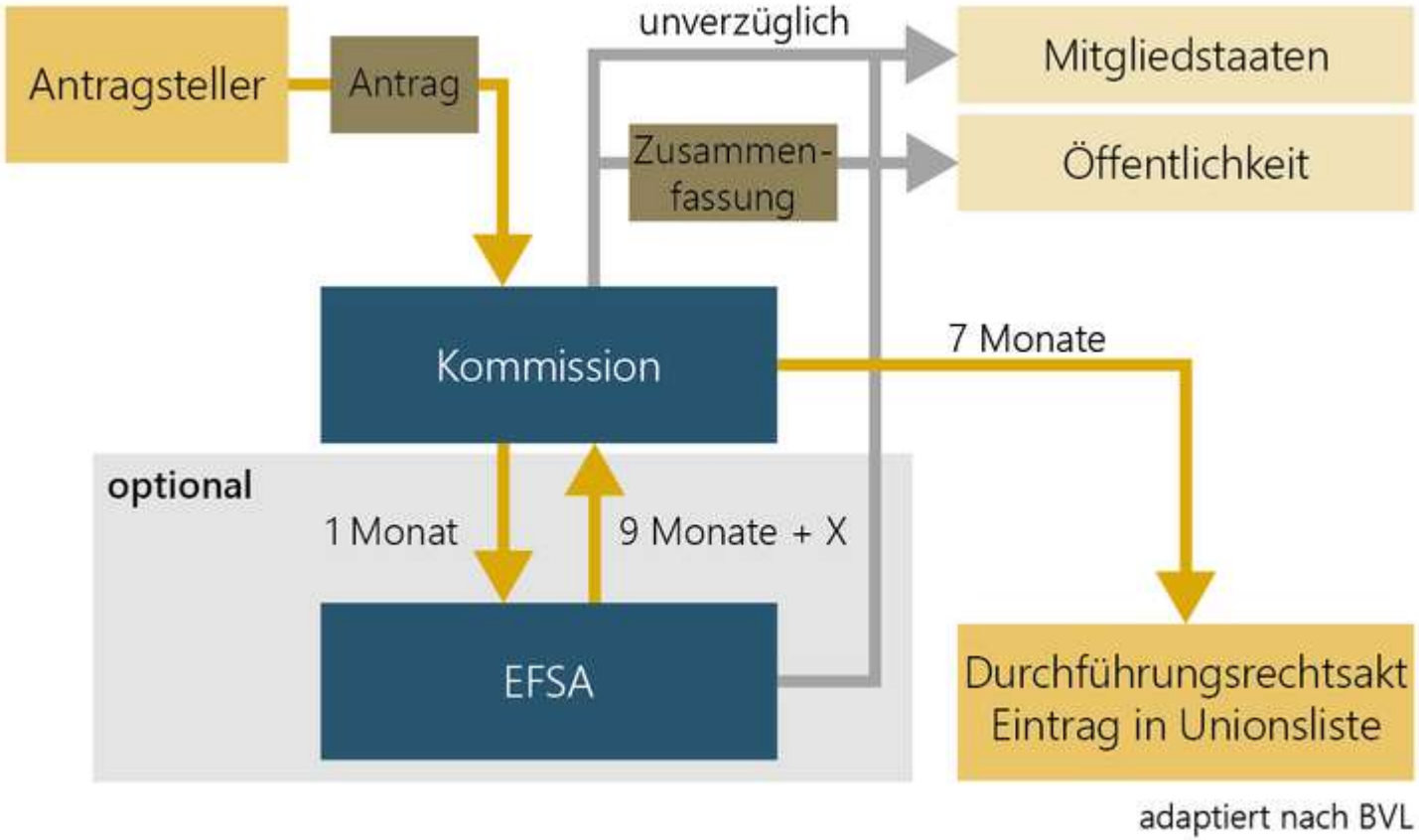
Improved shelf life

Nutrient retention

Environmental friendly

Process efficiency

Authorisation process

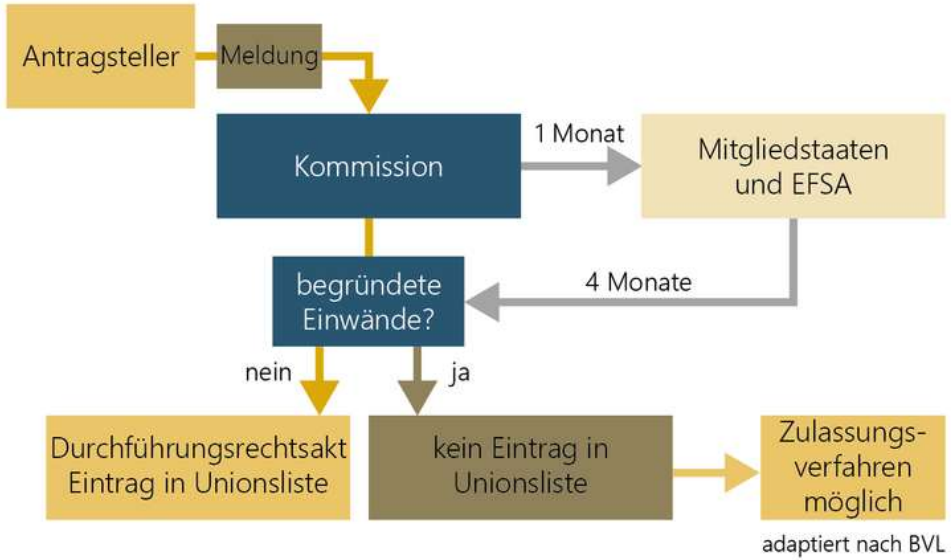


adaptiert nach BVL

Notification of a traditional food from third countries

There is facilitated market access into the EU for traditional foods from third countries. However a safe history of use of at least 25 years outside the EU has to be proven. But this only applies to plants, animals, micro-organisms, fungi, algae and cell and tissue cultures.

If there are no objections to the notification of the traditional food, it is entered on the Union list by means of an implementing act. In case of safety concerns, an authorisation procedure with shorter deadlines is possible (Article 16). EFSA has also published guidance on the notification of traditional foods from third countries. The procedure for notification of a traditional food is regulated in the Implementing Regulation (EU) 2017/2468. Currently ongoing applications for authorisation of a novel food as well as a traditional food from third countries can be viewed online at the European Commission.



Examples, Stevia

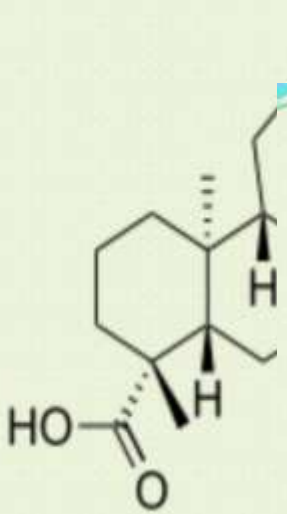
Stevia

Historical Background:

Stevia has been used over centuries by the Guaraní people of Brazil and Paraguay, who called it *ka'a he'ẽ* ("sweet herb"), to sweeten the local yerba mate tea, as medicine, and as a "sweet treat"

In 1899, botanist Moisés Santiago Bertoni first described the plant as growing in eastern Paraguay, and observed its sweet taste.

In 1931, chemists M Bridel and R Lavielle isolated the glycosides stevioside and rebaudioside that give the leaves their sweet taste. The exact structures of the aglycone steviol and its glycosides were published in 1955.



Novelty

- In 1991, the FDA refused to approve stevia as a sweetener as an additive in foods. However, in 2008, after the purification process was developed and patented by Coca-Cola, the FDA approved the stevia extracts as GRAS.
- Based on the JECFA (Joint Expert Committee on Food Additives) declaration, safe consumption of steviol glycosides for humans is determined to be 4 mg per kg body weight per day.
- It was also agreed by the European Commission in 2011 for use in food in European countries. Steviol glycosides have also been accepted in the US as GRAS (Generally Recognized as Safe).
- Stevia leaf and raw extracts are not treated as GRAS and their import into the US is not allowed for usage as sweeteners. Nutrition, Center for Food Safety and Applied (9 February2019). "Additional Information about High-Intensity Sweeteners Permitted for Use in Food in the United States". FDA.

- **Note:**
  Stevioside was found to be nontoxic in acute toxicity studies.

Lycopin

Lycopin - Herstellung

- Mit Hilfe spezieller, lebensmittelrechtlich zugelassener Lösungsmittel wird Lycopin aus Tomaten (*Lycopersicon esculentum* L.) extrahiert. Ein Kilogramm Tomaten enthält etwa 20 mg Lycopin.
- Häufiger als der isolierte Farbstoff wird Tomaten-Extrakt eingesetzt. Er gilt, wenn nicht der enthaltene Anteil Lycopin gezielt erhöht wurde, als färbendes Lebensmittel. Wenngleich Tomaten-Extrakt keine E-Nummer trägt, ist er doch in der Zutatenliste aufgeführt.
- Lycopin kann auch chemisch-synthetisch hergestellt werden. Gemäß einer Stellungnahme des Wissenschaftlichen Lebensmittelausschusses der EU vom Dezember 1999 darf synthetisches Lycopin jedoch nicht als Zusatzstoff eingesetzt werden (SCF/CS/ADD/COL/160 Final). Dies wird damit begründet, dass das synthetische Präparat anders als das durch Extraktion gewonnene zusammengesetzt sei und entsprechende toxikologische Untersuchungen bisher fehlten.

LM ethnic

2.7 Produkte aus fremden Kulturkreisen

- Noni-Saft (Fruchtsaft aus *Morinda citrifolia*)
  - Taxonomie, traditionelle Verwendung
  - Herstellung und Verwendungszweck
  - Wirkungsbehauptungen
  - Sicherheitsbewertung von Noni-Saft
- Nangai-Nüsse (Canarium indicum L.) aus südpazifischen Anbau
  - Taxonomie, traditionelle Verwendung
  - Sicherheitsbewertung von Nangai-Nüssen
  - Entscheidung der Kommission vom 19. Dezember 2000 zum Verbot des Inverkehrbringens von „Nangainüssen“ als neuartiges Lebensmittel

Sicherheitsbewertung

- In seiner Stellungnahme vom 4. Dezember 2002 war der SCF zu der Auffassung gelangt, dass Tahitian Noni®-Saft in den beobachteten Verzehrsmengen akzeptabel ist.
- Die EFSA hat am 6. September 2006 erneut die Sicherheit von Noni-Saft bewertet. Sie war von der Europäischen Kommission um eine wissenschaftliche Stellungnahme gebeten worden. Sie sollte bewerten, ob die berichteten Fälle von akuter Hepatitis einen Einfluss auf die Sicherheit von Noni-Saft haben würden.
- Noni-Saft ist seit 2003 als neuartiges Lebensmittel zugelassen, vermarktet zu werden. Das NDA-Gremium der EFSA kam zu dem Ergebnis, dass es keine schlüssigen Beweise für einen kausalen Zusammenhang zwischen der in den berichteten Fällen beobachteten akuten Hepatitis und dem Verzehr von Noni-Saft gibt.
- Unter Berücksichtigung der verfügbaren Informationen ist es unwahrscheinlich, dass der Verzehr von Noni-Saft in den festgestellten Verzehrsmengen unerwünschte Nebenwirkungen auf die menschliche Leber auslösen könnte.

Baobab

2.7 Baobab-Fruchtfleisch

Taxonomie, traditionelle Verwendung

- Der Baobab, *Adansonia digitata* Linné (1753), wird zur Familie der *Bombacaceae* (Wollbaumgewächse) gezählt. Häufig wird er auch als Affenbrotbaum bezeichnet, da die Früchte gern von Affen gefressen werden.
- Früchte und auch andere Teile (Samen, Wurzeln, Blätter, Blüten und Rinde) des Affenbrotbaumes werden von der afrikanischen Bevölkerung traditionell vielseitig verwendet.

Sicherheitsbewertung

- Antragsteller hat die traditionelle Verwendung durch Informationen aus der publizierten Literatur sowie aus gezielten Befragungen belegt.
- Es sind - abgesehen von einem laxierenden Effekt bei hohen Aufnahmemengen – keine schädlichen Wirkungen durch Verzehr von getrocknetem Baobab-Fruchtfleisch bekannt geworden.
- Aufgrund der langjährigen Lebensmitteltradition von Baobab-Früchten außerhalb Europas hält der Antragsteller die Sicherheit des Verzehrs von Baobab-Früchten für belegt und weiterführende Studien zur Verträglichkeit und Toxizität nicht für erforderlich.
- Die zuständige Lebensmittelprüfstelle des Vereinigten Königreiches kam in ihrem Bericht vom 12.7.2007 zu dem Schluss, das getrock-netes Baobab-Fruchtfleisch in den vorgeschlagenen Verwendungs-mengen für den menschlichen Verzehr unbedenklich ist.

The following facts should be taken into consideration:

- **Analytical/compositional and nutritional characteristics of the novel food (including its fate in biological systems);**
- **Previous history of human exposure;**
- **Expected applications as a novel food and the predicted exposure;**
- **Necessity, appropriateness and outcome of animal studies and studies in humans;**
- **Necessity and outcome of post-launch monitoring**

Novel Food Catalogue

http://ec.europa.eu/food/food/biotechnology/novelfood/nfnetweb/mod_search/index.cfm

- lists products of plant and animal origin and other substances subject to the Novel Food Regulation, after EU countries and the Commission agree in the Novel Food Working Group.
- non-exhaustive, and serves as orientation on whether a product will need authorisation under the Novel Food Regulation.
- EU countries may restrict the marketing of a product through specific legislation. For information, businesses should address their national authorities.
- In some cases, it shows EU countries' history of use of food supplements and ingredients used exclusively in food supplements.
- If foods and/or food ingredients were used exclusively in food supplements, new uses in other foods require authorisation under the Novel Food Regulation.

Authorisations of novel foods and novel food ingredients by Commission Decisions

" the placing on the market of…as a novel food ingredient"

2013

- zeaxanthin
- an extension of use of Chia (Salvia hispanica) seed

2012

- bovine lactoferrin
- dihydrocapsiate
- Gamma-Cyclodextrin
- novel chewing gum base

2011

- novel chewing gum base
- yeast beta-glucans
- Phosphatidylserine from soya phospholipids
- fermented black bean extract
- phosphated maize starch
- Chromium Picolinate
- chitin-glucan from Aspergillus niger
- mycelial extract from Lentinula edodes (Shiitake mushroom)
- Chromium Picolinate ingredient
- a fish (Sardinops sagax) peptide product
- a chitin-glucan from Aspergillus niger
- a mycelial extract from Lentinula edodes (Shiitake mushroom)

2010

- ferrous ammonium phosphate
- Ferric Sodium EDTA
- puree and concentrate of the fruits of Morinda citrifolia (Noni)

2009

- Chia seed (Salvia hispanica)
- a leaf extract from Lucerne (Medicago sativa) *sinimailanen*
- the uses of algal oil from the micro-algae Schizochytrium sp.
- the uses of algal oil from the micro-algae Ulkenia sp.
- a lipid extract from Antarctic Krill Euphausia superba
- lycopene
- lycopene from *Blakeslea trispora*
- lycopene oleoresin from tomatoes
- lycopene as a novel food ingredient
- Ice Structuring Protein type III HPLC 12
- Vitamin K2 (menaquinone) from *Bacillus subtilis natto*

2008

- leaves of Morinda citrifolia (Noni)
- arachidonic acid-rich oil from Mortierella alpina (belong to soil fungi)
- Baobab dried fruit pulp (a tree native to Africa, Australia, Madagaskar, Arabian Peninsula)
- allanblackia seed oil (flowering plant in the Clusiaceae family, African)
- refined echium oil (a genus of 60 species of flowering plant in the family Boraginaceae. Native to North Africa, mainland Europe and the Macaronesian islands)
- alpha-cyclodextrin
- rice drinks with added phytosterols/phytostanols (Teriaka Ltd)

2006-2007

- oil enriched with phytosterols/phytostanols
- diacylglycerol oil of plant origin
- lycopene from Blakeslea trispora
- rapeseed oil high in unsaponifiable matter
- maize-germ oil high in unsaponifiable matter“
- foods and food ingredients derived from genetically modified maize line MON 863
- rye bread with added phytosterols/phytostanols (Fazer, Pharmaconsult)
- foods and food ingredients produced from genetically modified Roundup Ready maize line GA21

2004-2005

- isomaltulose
- foods and food ingredients derived from genetically modified maize line NK 603
- milk based beverages with added phytosterols/phytostanols
- sweet corn from genetically modified maize line Bt11
- yellow fat spreads, milk based fruit drinks, yoghurt type products and cheese type products with added phytosterols/phytostanols (Teriaka Ltd)
- milk type products and yoghurt type products with added phytosterol esters
- yellow fat spreads, milk type products, yoghurt type products, and spicy sauces with added phytosterols/phytostanols (Pharmaconsult Oy Ltd. (formerly MultiBene Health Oy Ltd))
- yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks and cheese type products with added phytosterols/phytostanols

2000-2003

- Salatrim
- oil rich in DHA
- 'noni juice'
- coagulated potato proteins and hydrolysates thereof
- dextran preparation produced by Leuconostoc mesenteroides.
- pasteurised fruit-based preparations produced using high-pressure pasteurisation.
- trehalose
- "yellow fat spreads with added phytocolesterol esters"
- "phospholipides from egg yolk"

Refusals of authorisation of novel foods and novel food ingredients by Commission Decisions

2000-2005

- Betaine

- "Nangai nuts" *Canarium indicum* L (dried seed kernels)
  http://old.eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:004:0035:0035:EN:PDF

- *Stevia rebaudiana Bertoni* plants and dried leaves
  http://old.eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:061:0014:0014:EN:PDF

Note! Usage of steviol glycosides from leaf extracts as sweeteners has been accepted (since 2.12.2011, EU food additive legislation)

Points to consider (from Hermann M. The impact of the European Novel Food Regulation on trade and food innovation based on traditional plant foods from developing countries. Food Policy 34 (2009) 499-507.)

- Market access outside EU (many of the novel foods available in Canada, USA, Switzerland and Japan), re-directing of the marketing due to restrictions in Europe?

- Importance of traditional exotic foods to the economics of poor countries and to the diet diversification among EU consumers? The regulation is critized being a non-tariff trade barrier for food that is "exotic" from the EU perspective.

- Would separate categories be needed for exotic traditional foods and "true" novel, innovative foods with no long-term consumption outside the EU?
  - Now extensive data is required of composition, nutritional aspects, intake, toxicology and allergenic potential, also for products that are generally regarded as safe (GRAS) outside the EU
  - Are the requirements even stricter than those required for accepted traditional European foods?
  - Are the scientific requirements proportionate to the potential risks they pose?
  - Currently, the history of safe use outside the EU is not considered - should traditional knowledge be admitted for food safety assessment?
  - Lack of peer-reviewed publications, lack of data from certified laboratories – should be taken into account in project design, product development and trade promotion
  - Traditional knowledge from the local people should be used.

- Would the potato be authorized nowadays (glycoalcaloids)? Wheat (gluten)?

USA, FDA : no regulatons define Novel foods

How are Novel Foods defined by the Food and Drug Administration?

The United States of America (USA) has different regulatory classification systems and pre-market approval processes. In the United States, no regulation defines "Novel Foods"; however, any new food ingredient is considered either as a food additive or Generally Recognized as Safe (GRAS).

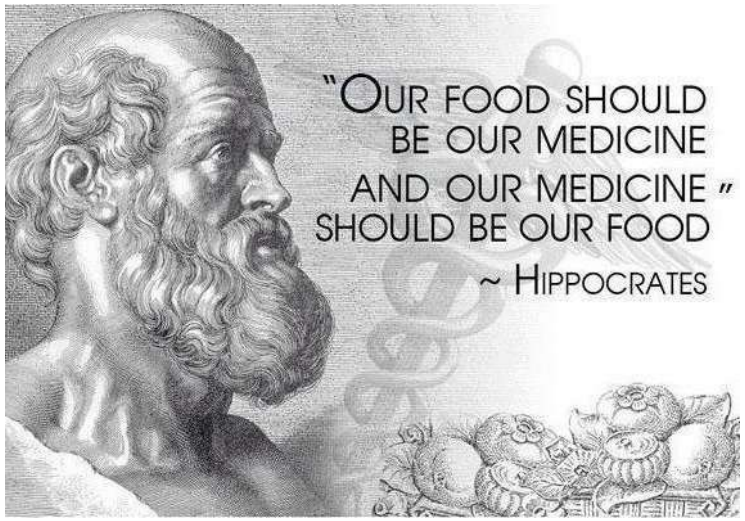
A food additive is any substance that is reasonably expected to become a component of food either directly or indirectly; these require pre-market approval. In this case, the applicant needs to submit a Food Additive Petition (FAP) to the USA Food and Drug Administration (FDA). A food additive is any substance that is reasonably expected to become a component of food either directly or indirectly; these require pre-market approval. In this case, the applicant needs to submit a Food Additive Petition (FAP) to the US FDA.

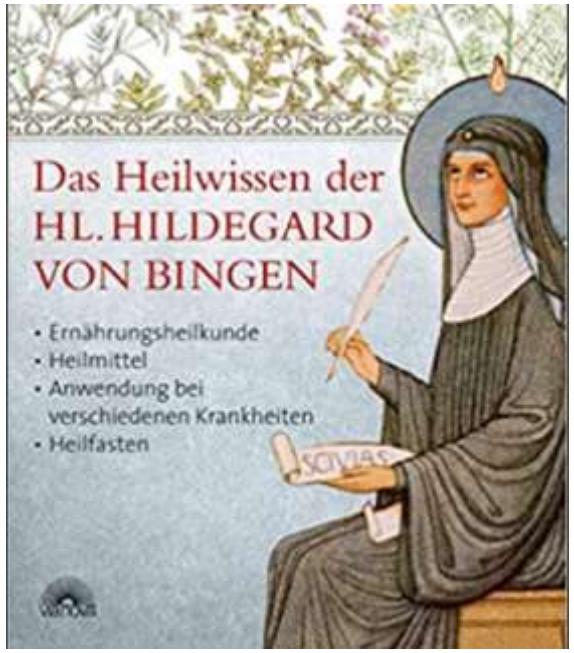
GRAS substances, on the other hand, are exempted from the definition of "food additive" and instead are defined as "*substances that are generally recognized, among experts qualified by scientific training and experience to evaluate their safety as having been adequately shown through scientific procedures to be safe under the conditions of their intended use.*"

Nutrition, disease prevention Functional foods, additives health claim regulation

- Lebensmittel vs. Arzneimittel?
  - Bei Pflanzen-Extrakten große kulturelle Unterschiede in den Mitgliedstaaten der EU
    Länder mit langer Tradition, aber sehr unterschiedlichen Handhabungen (pos. vs neg. Liste, LM vs. AZM)

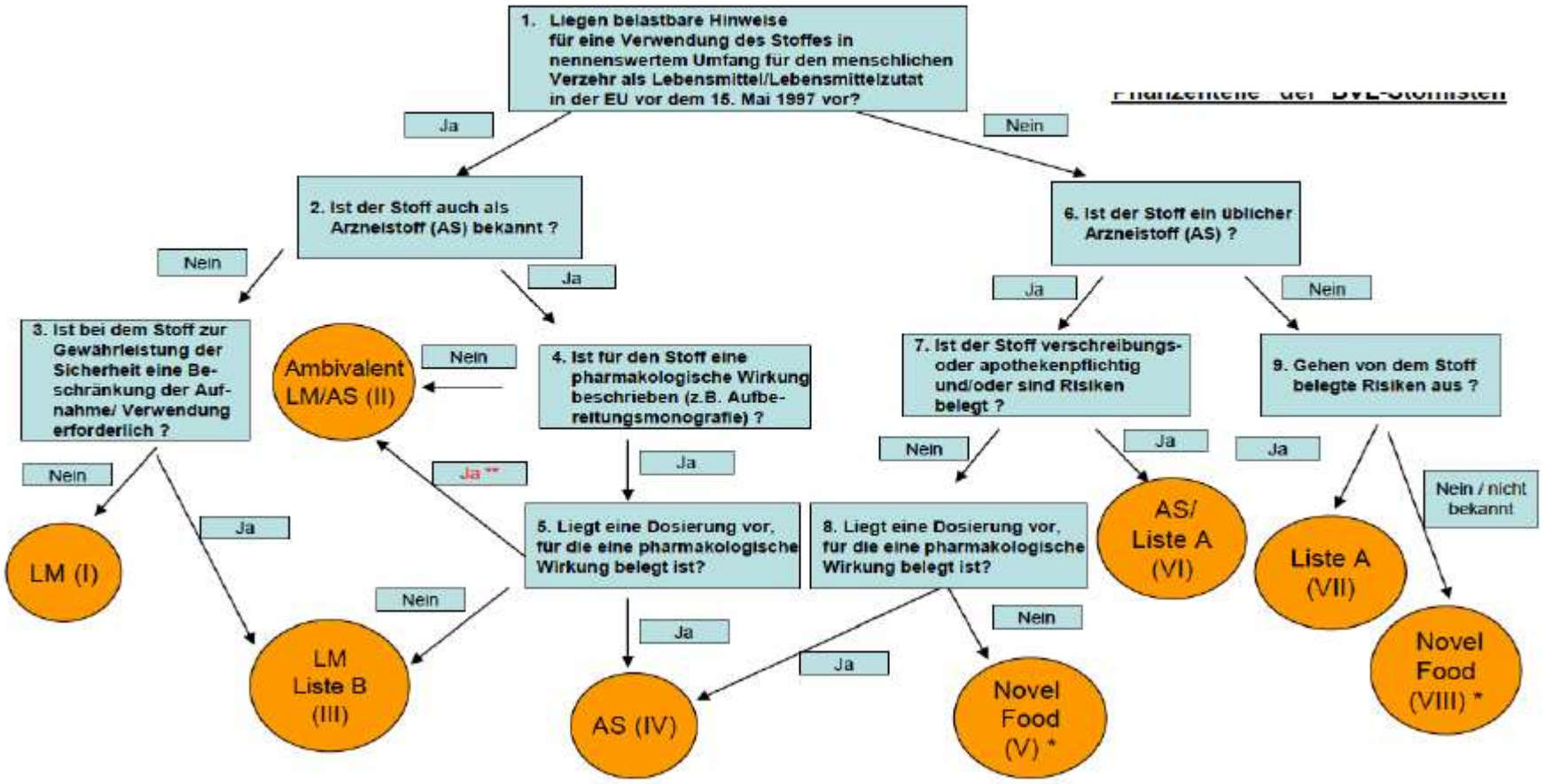
- Neuartig (Novel Food) oder nicht?
  - Vielfältige und nicht konsistente Interpretation sowohl auf Mitgliedstaaten als auch EU-Ebene
  - **Folge** → große Unsicherheiten, eingeschränkte Entwicklungsmöglichkeiten



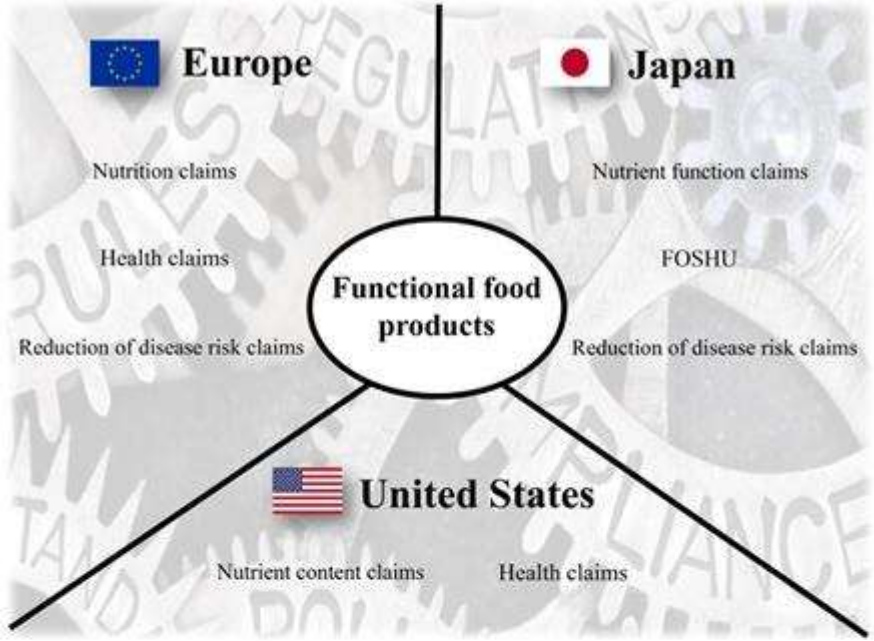


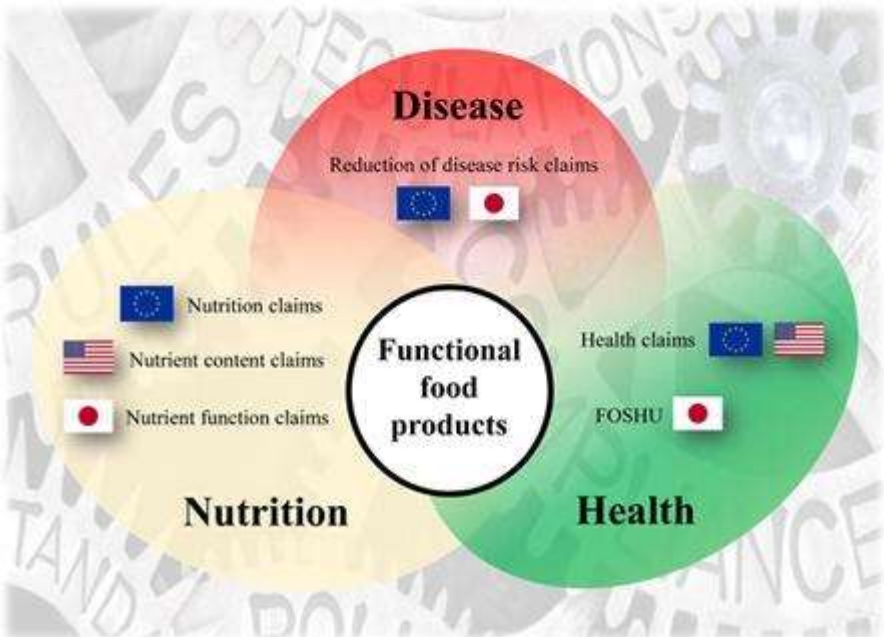
Food or medicine ?

Entscheidungsbaum zur Einstufung von „Pflanzen und Pflanzenteile“ („Botanicals“) in die Kategorien „Lebensmittel“, „Arzneistoff“ und „Neuartige Lebensmittel(zutaten)“

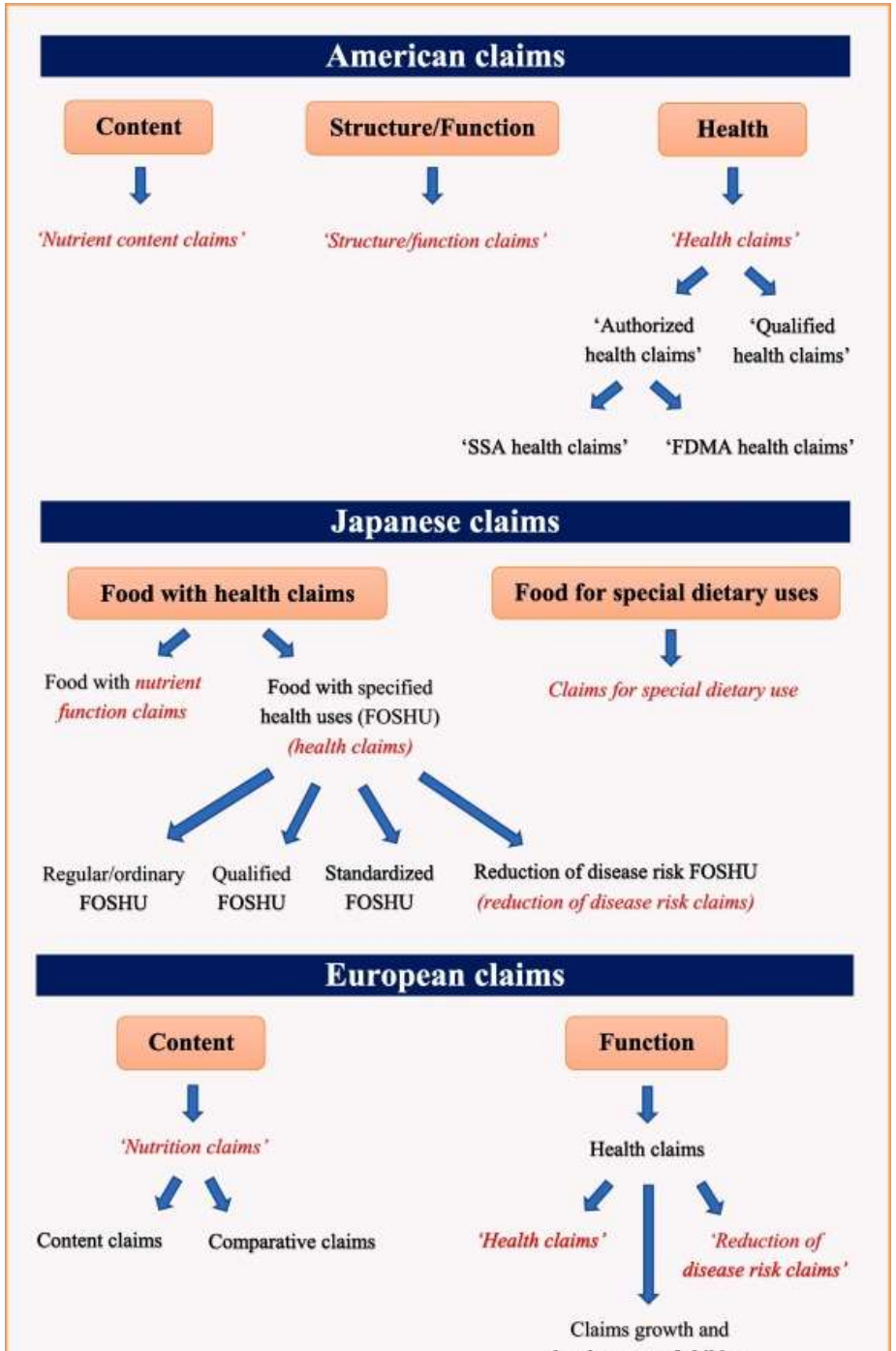


Kennzeichnung claims Regional differences

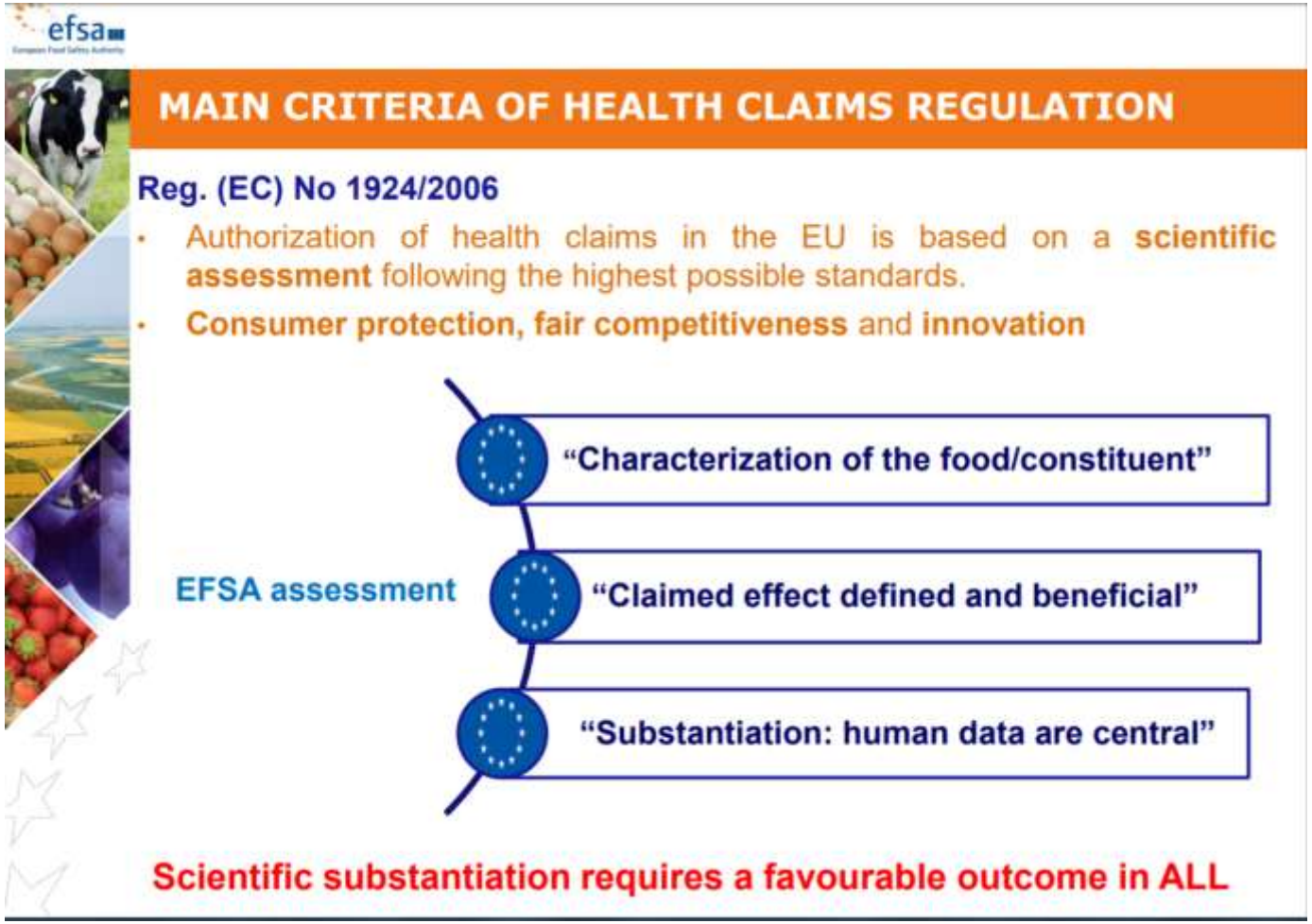




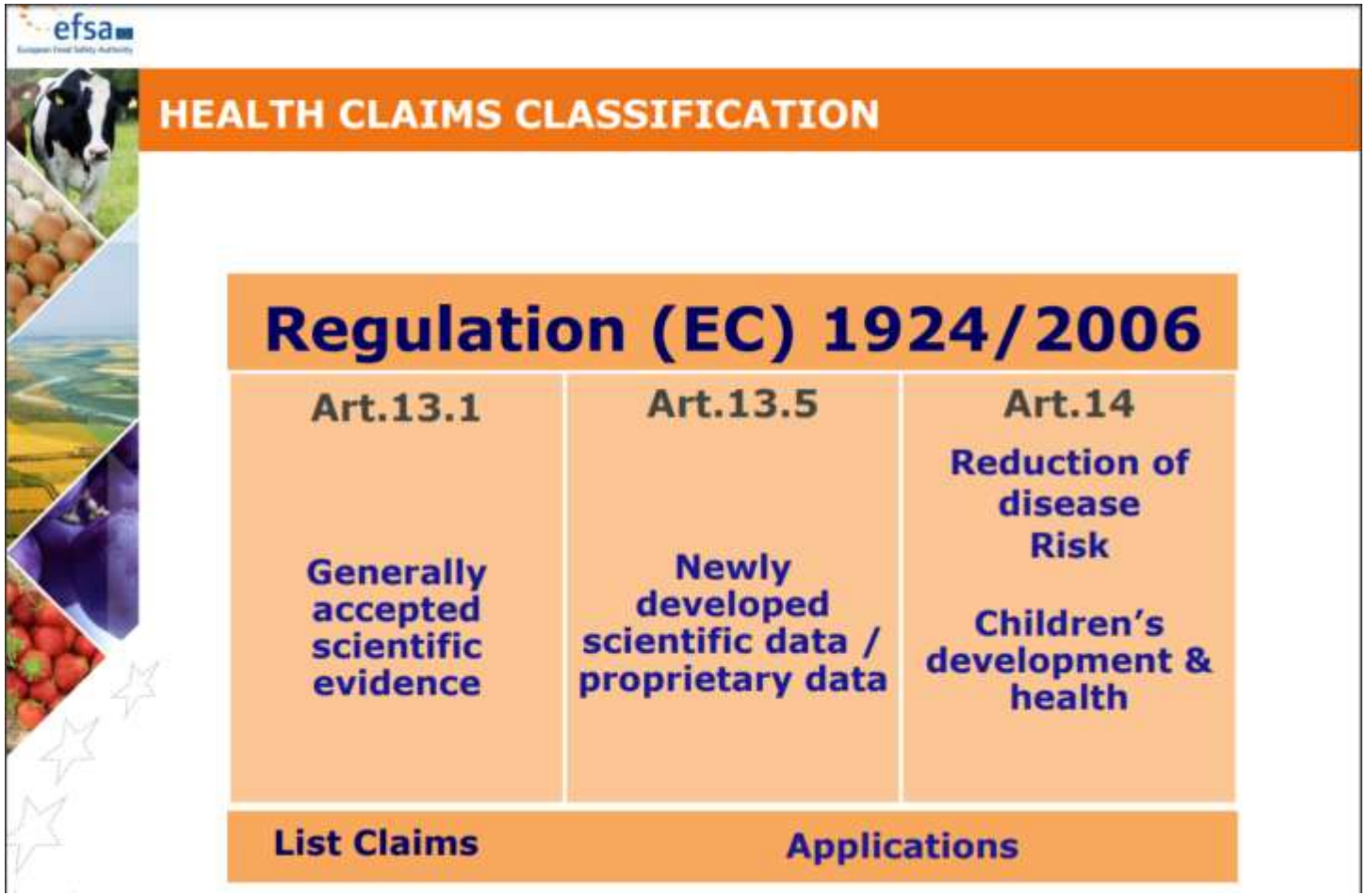
Regional differences



Health claim regulation



Health claim classification



Examples 13.1

FAVORABLE HEALTH CLAIMS (ART 13.1)

Out of **421** IDs related to this area: **42 with favourable outcomes**

- ✓ **14** related to immune function (essential nutrients i.e.: copper, folate, iron, selenium, vit D, A, B12, B6, C, and zinc)
- ✓ **15** related to GI function
  - ➢ **10 bowel function (e.g. dried prune, lactulose, wheat bran fibre, rye fibre, oat and barley grain fibre)**
  - ➢ 4 GI discomfort caused by lactose intake in lactose intolerant (e.g. foods with reduced lactose content)
  - ➢ 1 reduction of intestinal gas accumulation (e.g. *Activated charcoal*)
- ✓ **13** related to absorption/digestion
  - ➢ 7 Absorption of micronutrients (e.g. Vit C, D, meat or fish, fats)
  - ➢ 2 Digestion (e.g. Ca, chloride)
  - ➢ 4 **lactose digestion**:

  (i.e. lactase, **live yoghurt cultures**)

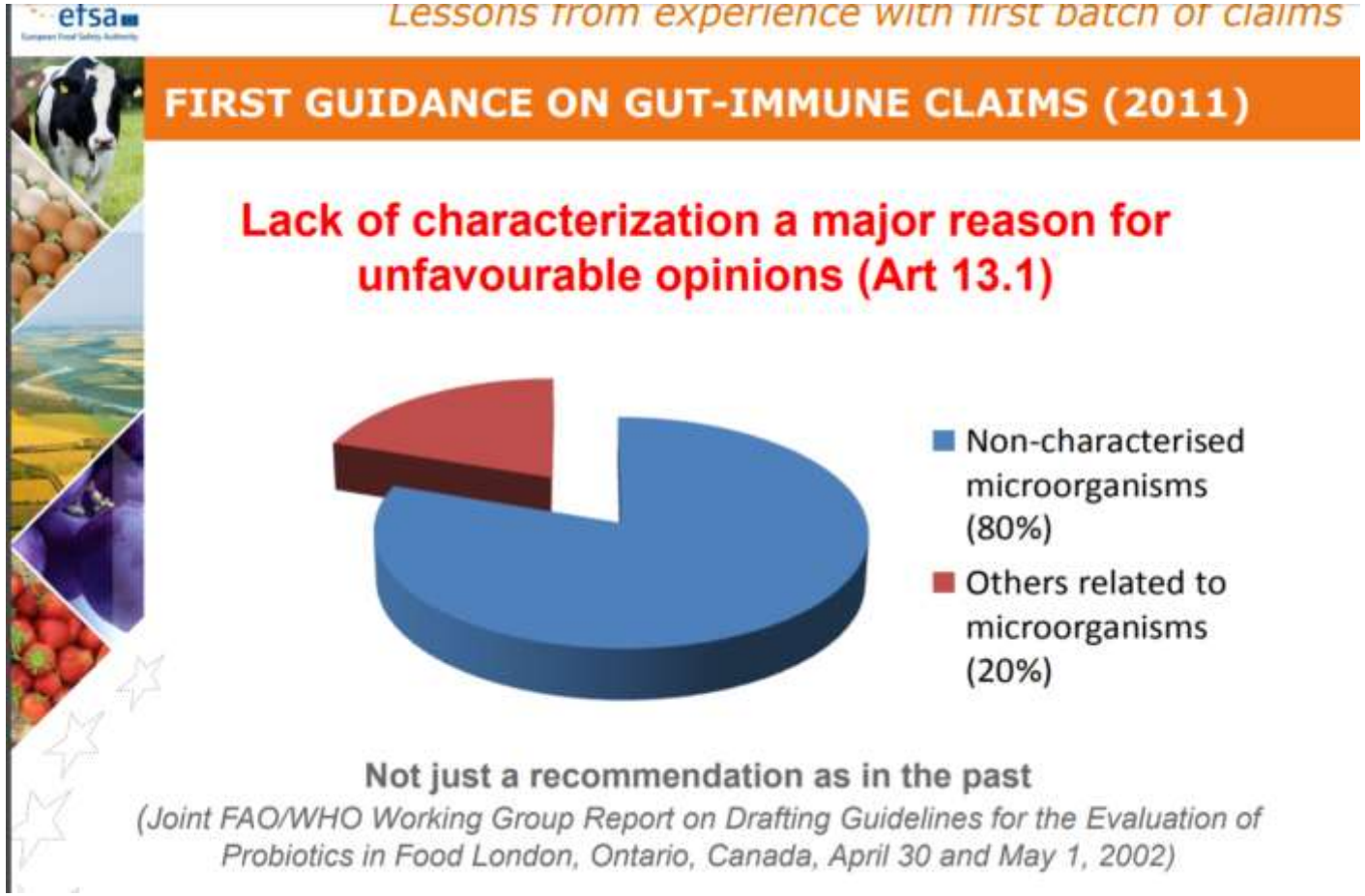
Examples 13.5

FAVORABLE HEALTH CLAIMS (ART 13.5, 14)

Of 155 applications related to this area (07/2015):

- ✓ 7 applications under evaluation or validation
- ✓ 90 applications withdrawn during the evaluation
- ✓ **58** applications with opinions adopted/published
  - ✓ 1 with the food not characterised
  - ✓ 5 with insufficient evidence
  - ✓ 45 with cause and effect relationship not established
  - ✓ **7 with favourable outcomes:**
    - 3 Immune system (e.g. Vitamin D, Zinc)
    - 3 **bowel function (i.e. sugar beet fibre) chicory inulin, hydroxyanthracene derv.)**
    - 1 Absorption of micronutrient (e.g. Vitamin C

Problems of gut immune claims (eg probiotoics



European Food Safety Authority

META-ANALYSIS FOR ASSESSING PROBIOTIC EFFECTS ?

Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea

A Systematic Review and Meta-analysis

Susanne Hempel, PhD
Sydne J. Newberry, PhD
Alicia R. Maher, MD

Context Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

The main limitation

to this result are residual unexplai
heterogeneity, poor documentatio
the probiotic strains, and lack of
sessment of probiotic-specific adv
events.

Conclusions The pooled evidence sug
reduction in AAD. More research is need
ciated with the greatest efficacy and fc
antibiotics.

JAMA. 2012;307(18):1959-1969

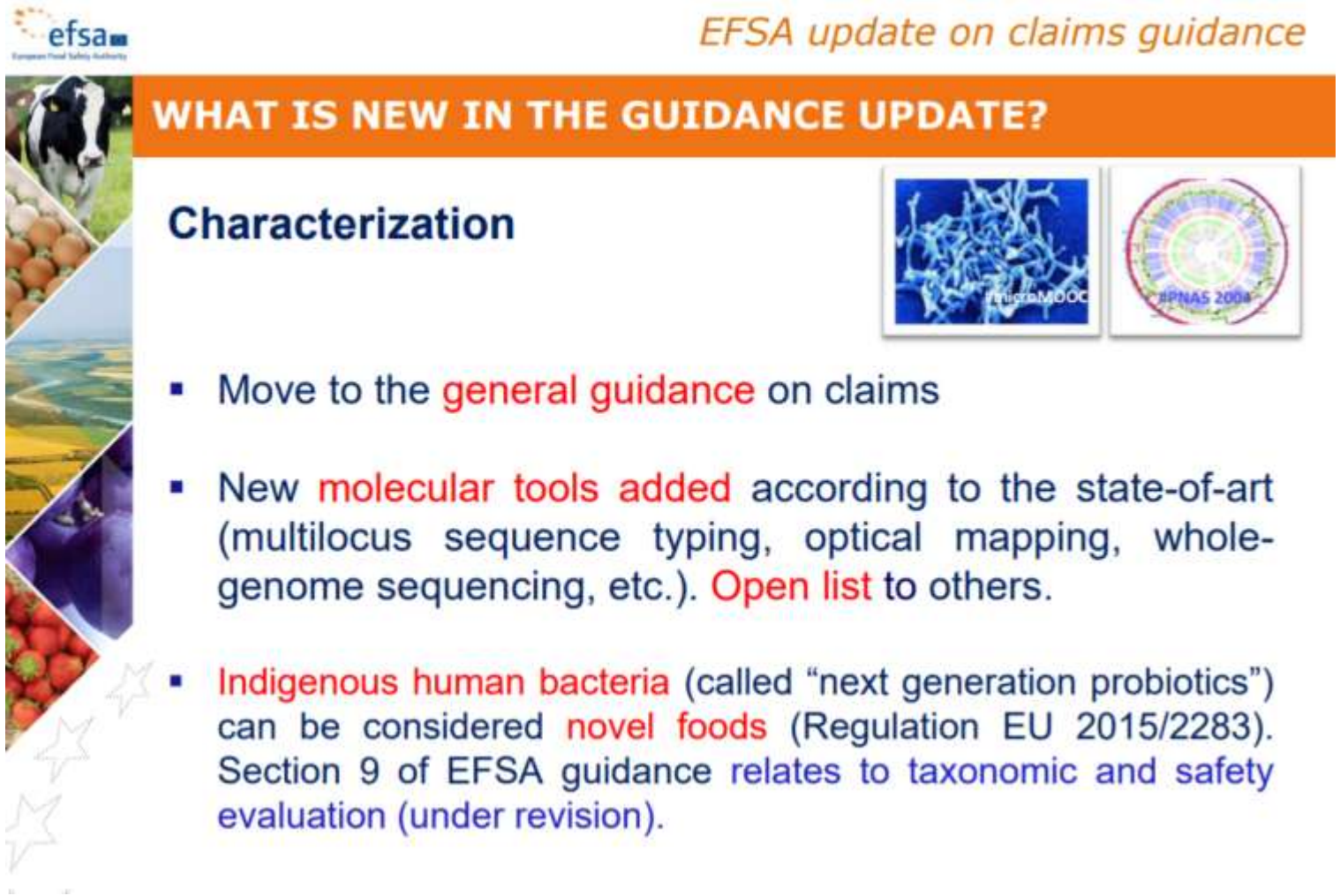
www.jama.com

General public health recommendations

≠

Commercial promotion of a brand/propietary strain through claims

New developmements



Spermidine

Scientific output

Scientific Opinion on the substantiation of health claims related to spermidine and contribution to normal hair growth (ID 1705) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

… Opinion on the substantiation of health claims related to **spermidine** and contribution to normal hair growth (ID 1705) … 10.2903/j.efsa.2011.2265 2265 Fri, 04/08/2011 - 12:00 **Spermidine** , hair growth, health claims European Commission …

Published: 30 June 2011

Scientific output

Scientific Opinion on the substantiation of a health claim related to spermidine and prolongation of the growing phase (anagen) of the hair cycle pursuant to Article 13(5) of Regulation (EC) No 1924/2006

… Opinion on the substantiation of a health claim related to **spermidine** and prolongation of the growing phase (anagen) of … 10.2903/j.efsa.2011.2466 2466 Wed, 11/23/2011 - 12:00 **Spermidine** , hair cycle, anagen, health claims Competent …

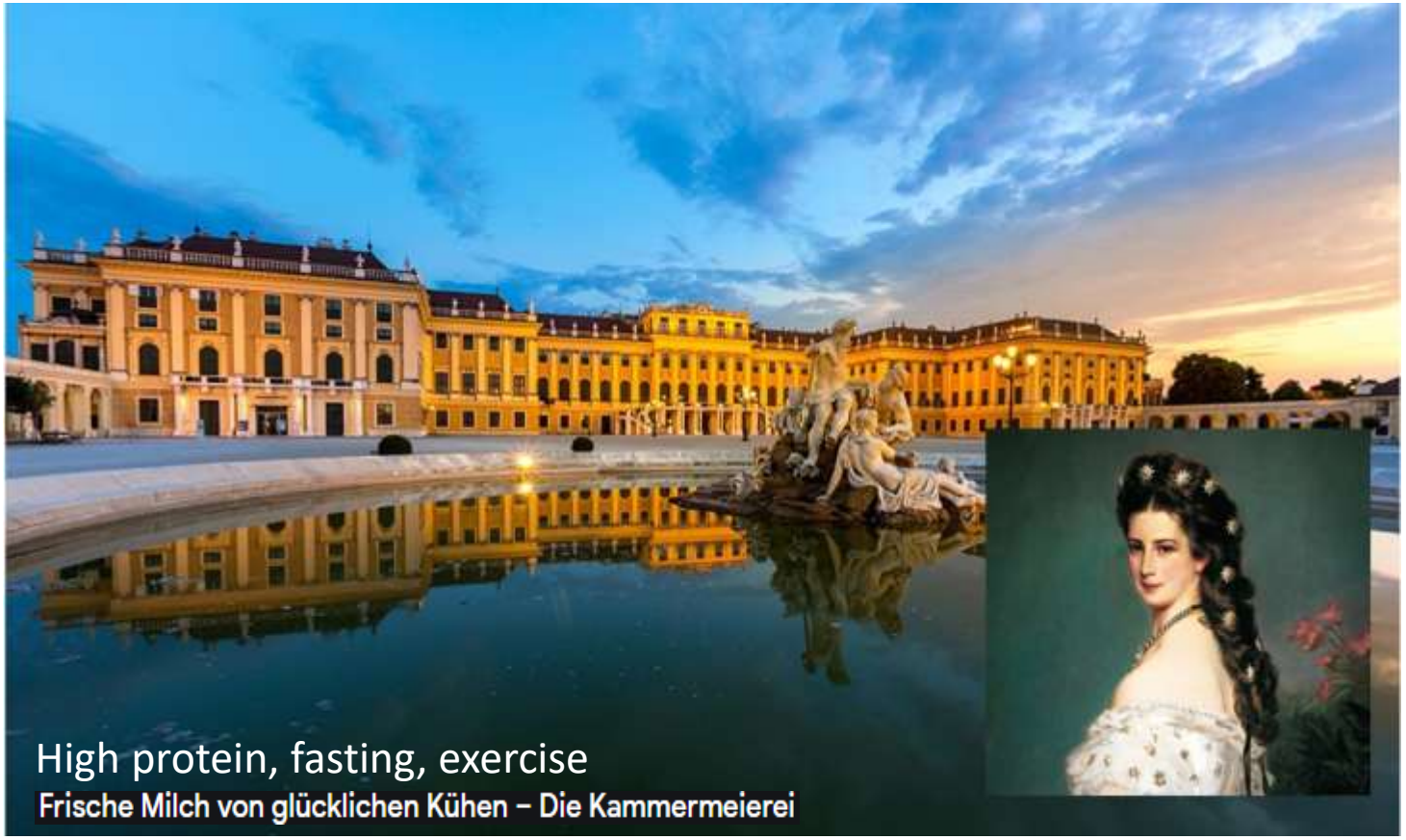
Published: 7 December 2011

Scientific output

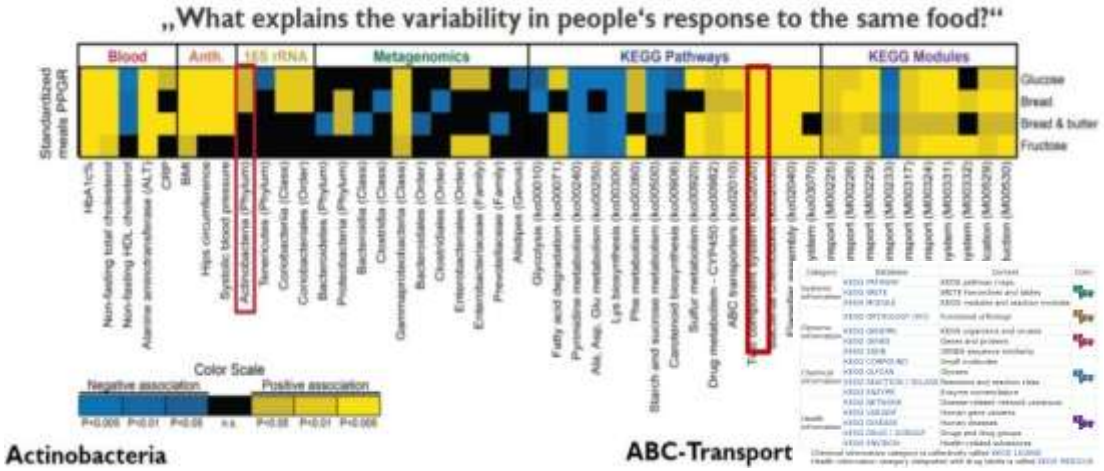
Response to comments on the Scientific Opinion on the substantiation of a health claim related to spermidine and prolongation of the growing phase (anagen) of the hair cycle pursuant to Article 13(5) of Regulation (EC) No 1924/2006

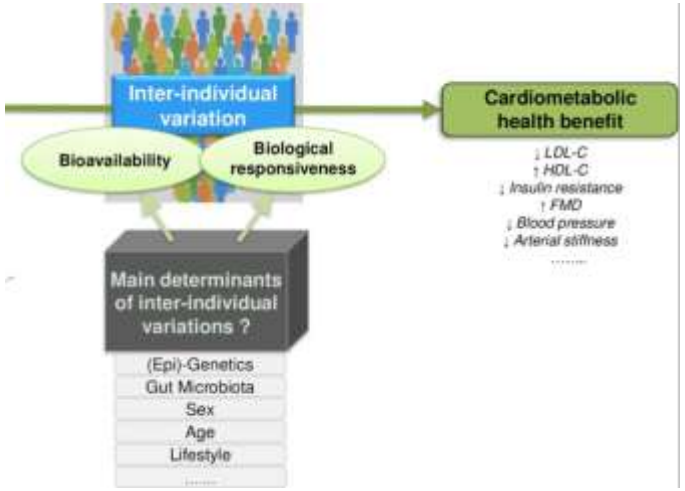
… Opinion on the substantiation of a health claim related to **spermidine** and prolongation of the growing phase (anagen) of … 10.2903/sp.efsa.2012.EN-309 EN-309 Fri, 06/29/2012 - 12:00 **Spermidine** , hair, health claims, comments European …

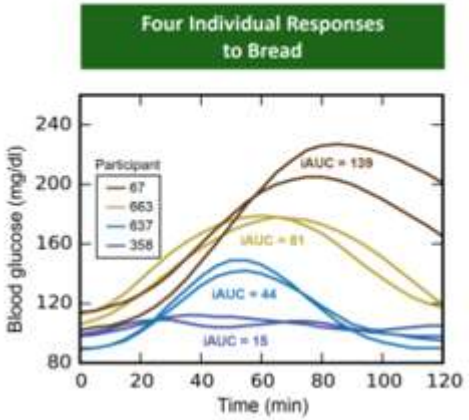
Personalisation and novel foods



Highly different personal responses to diets, eg post- prandial glycemic responses, explanations ?



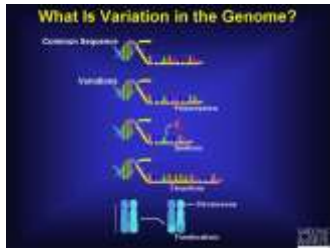


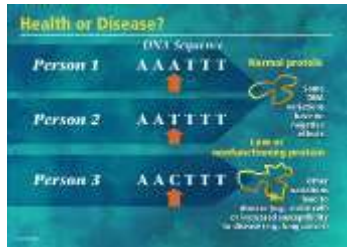


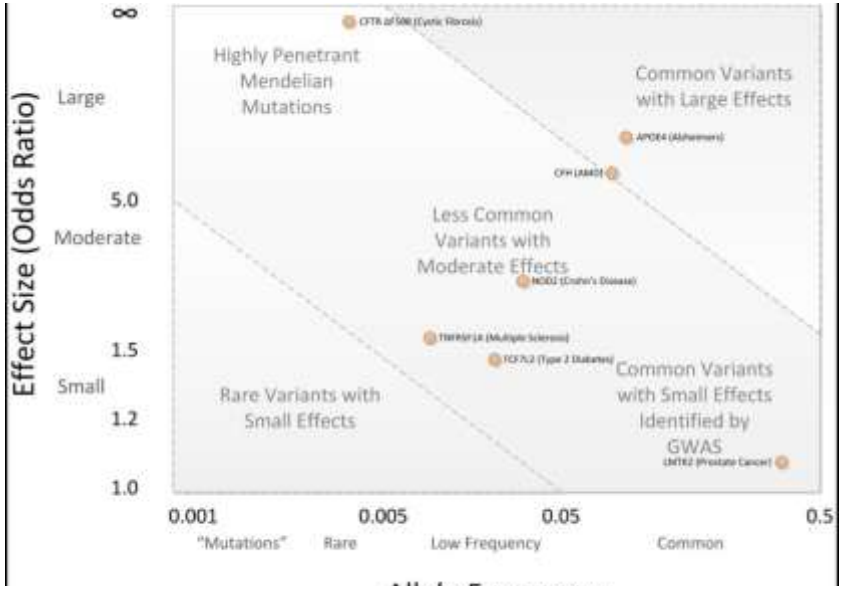
Different people have different, opposite responses to standardized meal, bread, Zeevi et al., 2015, Cell


Addressing the inter-individual variation in response to consumption of plant food bioactives: Towards a better understanding of their role in healthy aging and cardiometabolic risk reduction

GWAS : SNPs, common variants have often only moderate effects; in different metabolic areas





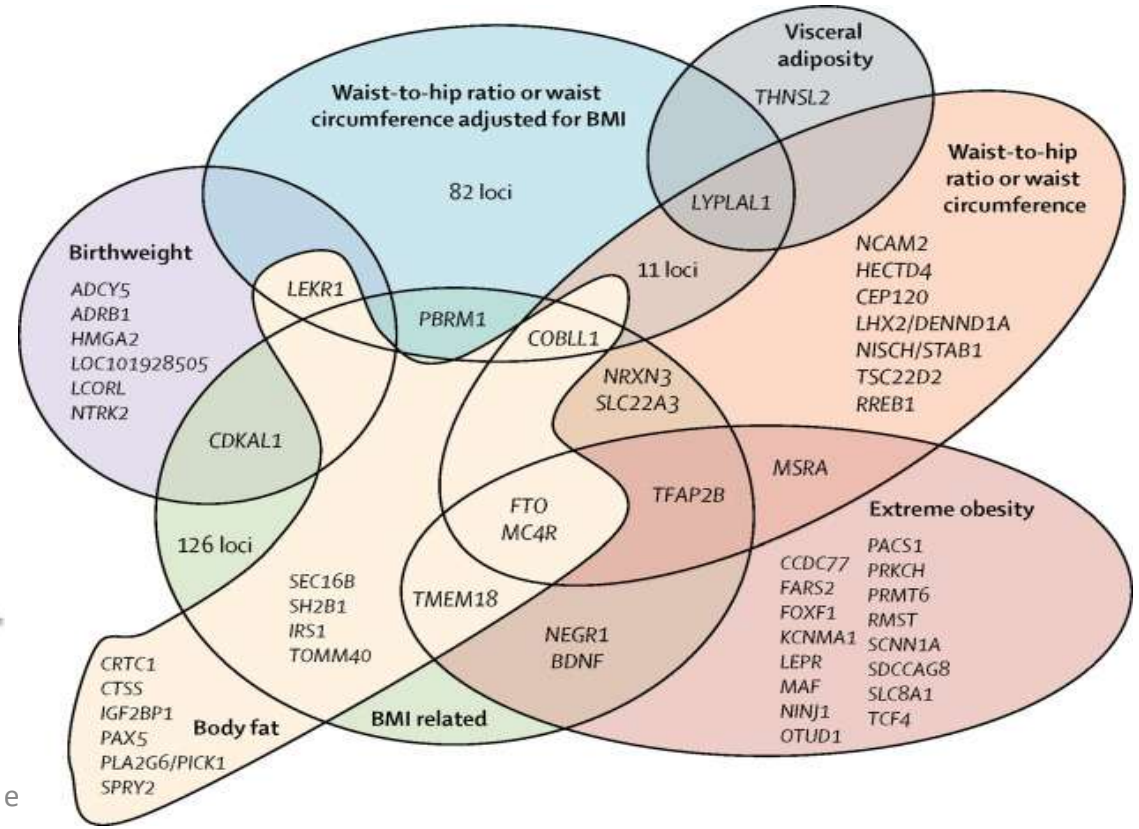


Methods

Prediction of individual genetic risk to disease from genome-wide association studies

Naomi R. Wray,[1,4] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

[1]Genetic Epidemiology, Queensland Institute of Medical Research, Queensland 4029, Brisbane, Australia; [2]Faculty of Land and Food Resources, University of Melbourne, Victoria 3010, Australia; [3]Department of Primary Industries, Victoria 3049, Australia



despite low penetrance of SNPs, D-T-C genetic testing for nutritional advice


COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

A survey of direct-to-consumer genotype data, and quality control tool (GenomePrep) for research

Chang Lu, Bastian Greshake Tzovaras, Julian Gough

For diseases controlled by 1000 loci of mean relative risk of only 1.04, a case-control study with 10,000 cases and controls can lead to selection of ~75 loci that explain >50% of the genetic variance. The 5% of people with the highest predicted risk are three to seven times more likely to suffer the disease than the population average, depending on heritability and disease prevalence. Whether an individual with known genetic risk develops the disease depends on known and unknown environmental factors.

But:
FTO+MC4R : 1.7 % increase in fat mass


Combined effects of MC4R and FTO common genetic variants on obesity in European general populations.

A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity.

1. Format check
- Accepts ASCII, gzip, zip, bzip2
- Parse 23andMe-like formats
- Parse VCF format

2. File sanity check
- Identify assembly
- Check against reference genome
- Reverse-strand
- Distinguish genotyping from NGS data

3. SNP sanity check
- Array cluster identification
- Genotyping SNP sanity check

7076 open genomes
5784 OpenSNP, 1292 PGP

95% (6720) 23andMe-like

1.5% (108) VCF-format

3.5% (248)
228 Invalid
- PDF, word etc. (119)
- Not genetic data (109)
20 Failed to parse

Passed genotyping data	6425
GRCh37	5812
GRCh36	604
GRCh38	9
Imputation	**17**
Failed	59
Assembly problem	3
Failed by similarity to reference	34
Failed by reverse strand	22
Incomplete	**219**
VCF genotyping	**54**
VCF NGS	**44**

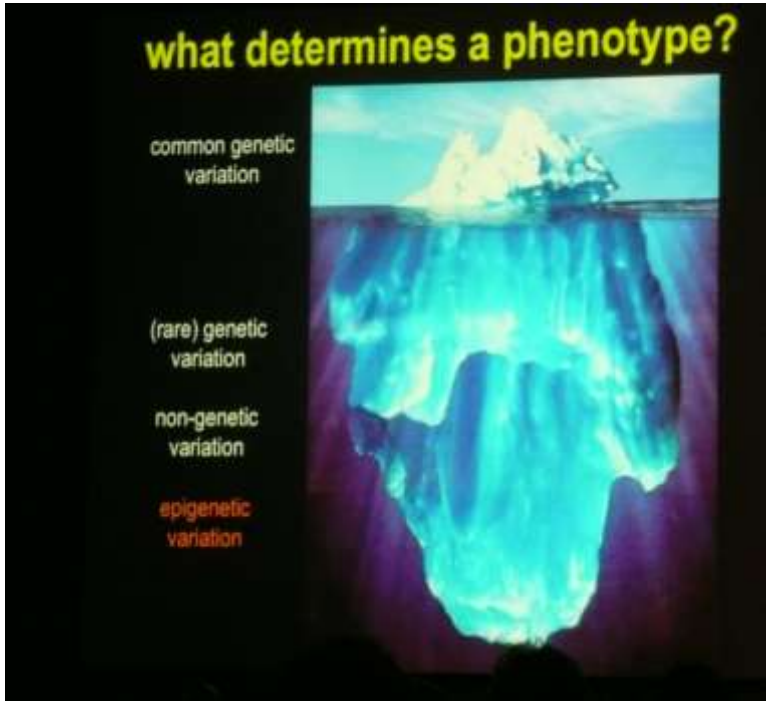
91.6% (6477) genotyping data

Cluster ID	Percentage
c1, 23andMe	35%
c3, ancestrydna-v1	13%
c4, 23andme, 1M	27%
c5, ancestrydna-v2	9%
v5, Illumina-GSA	15%
Un-clustered	<1% (56)

0.6% (44) NGS
0.2% (17) Imputation
3.1% (219) Incomplete
4.3% (307) Excluded

Melanocortin

Missing heritability: what is missing to understand a phenotype: gene- environment interactions, epigenetics, reversibility



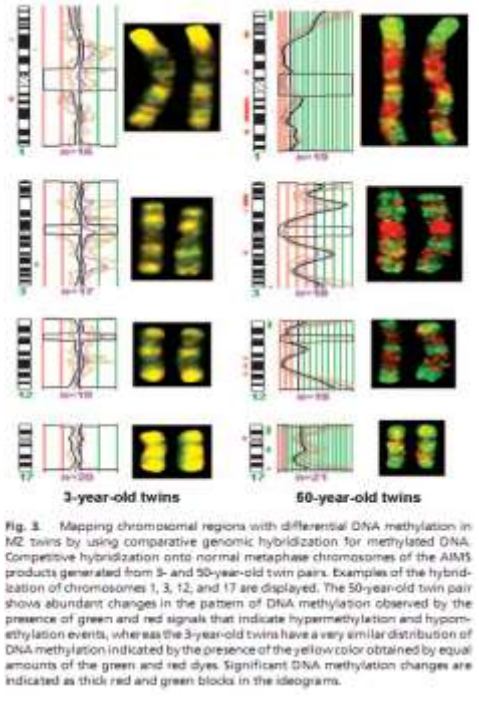
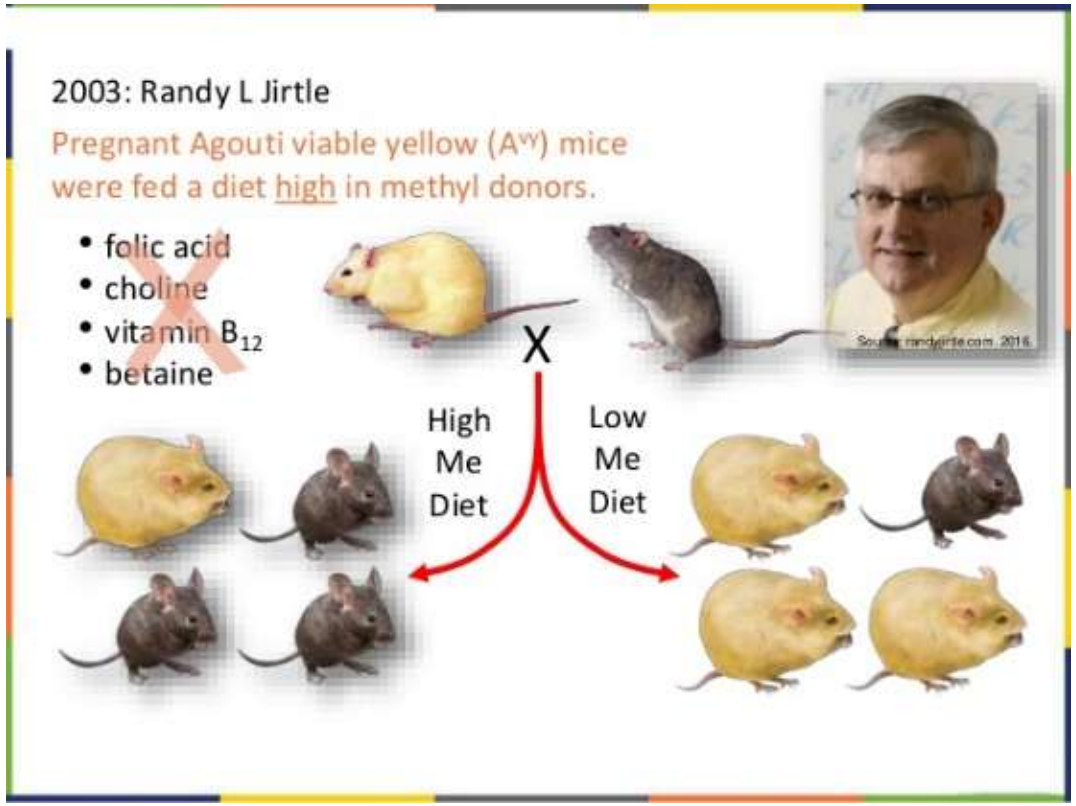
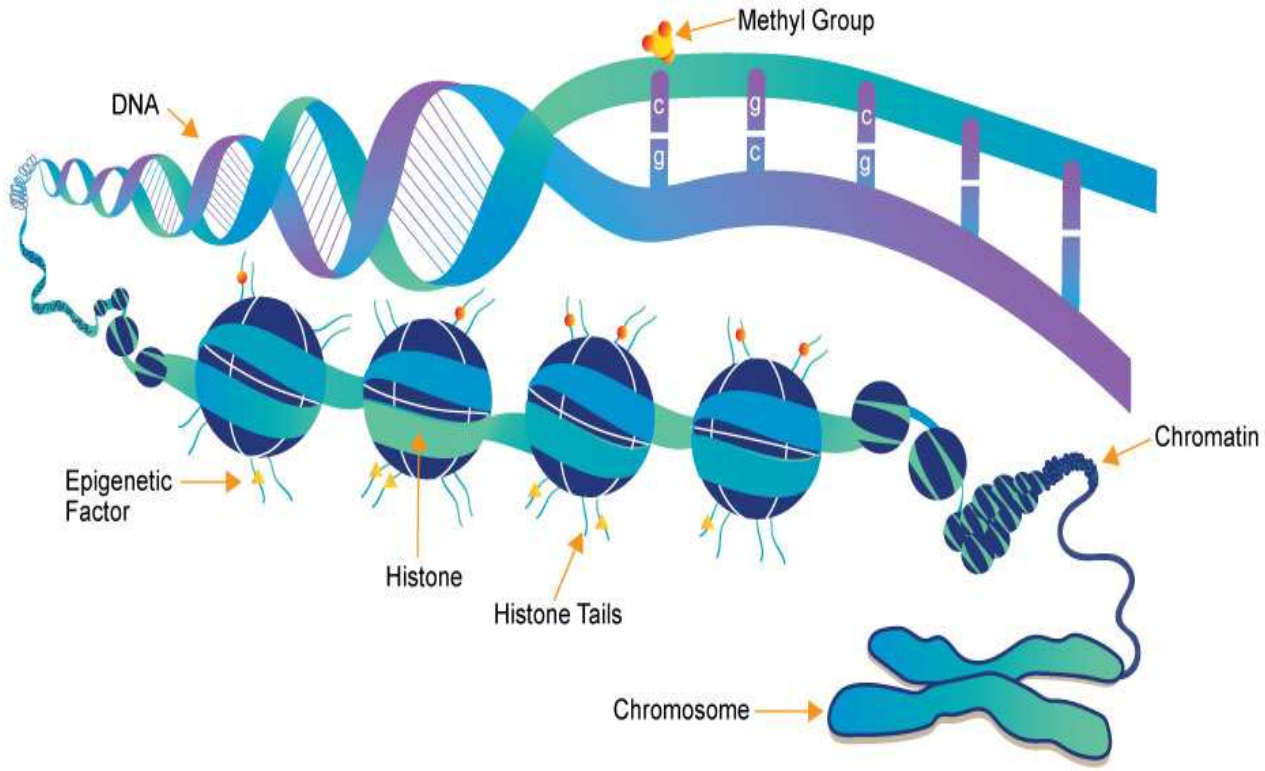
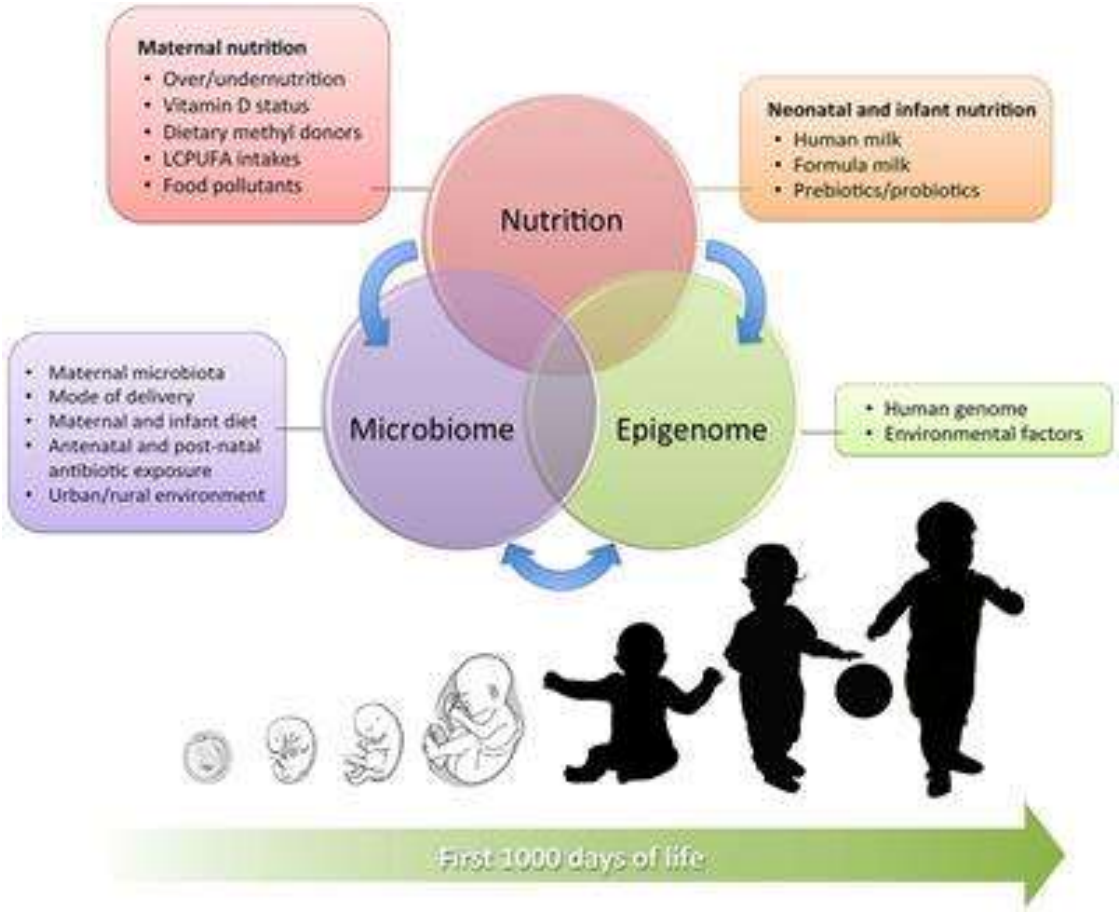


Fig. 3. Mapping chromosomal regions with differential DNA methylation in MZ twins by using comparative genomic hybridization for methylated DNA. Competitive hybridization onto normal metaphase chromosomes of the AIMS products generated from 3- and 50-year-old twin pairs. Examples of the hybridization of chromosomes 1, 3, 12, and 17 are displayed. The 50-year-old twin pair shows abundant changes in the pattern of DNA methylation observed by the presence of green and red signals that indicate hypermethylation and hypomethylation events, whereas the 3-year-old twins have a very similar distribution of DNA methylation indicated by the presence of the yellow color obtained by equal amounts of the green and red dyes. Significant DNA methylation changes are indicated as thick red and green blocks in the ideograms.

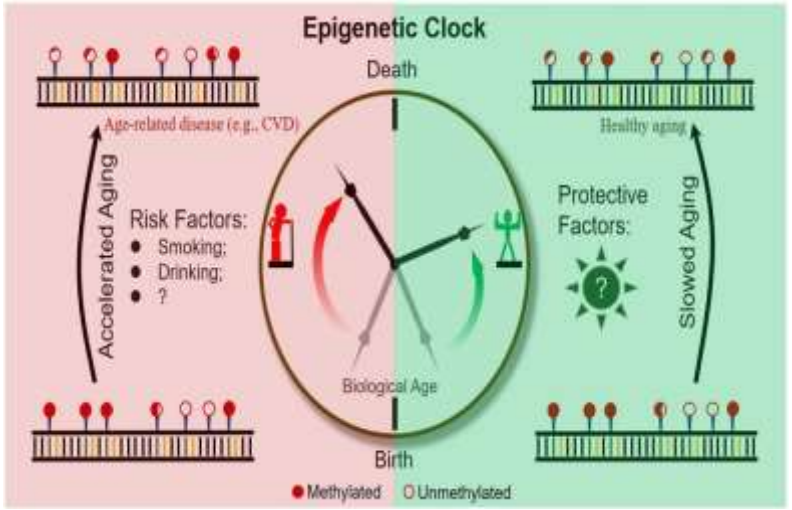


Epigenetics mechanisms, Interactions, early imprinting

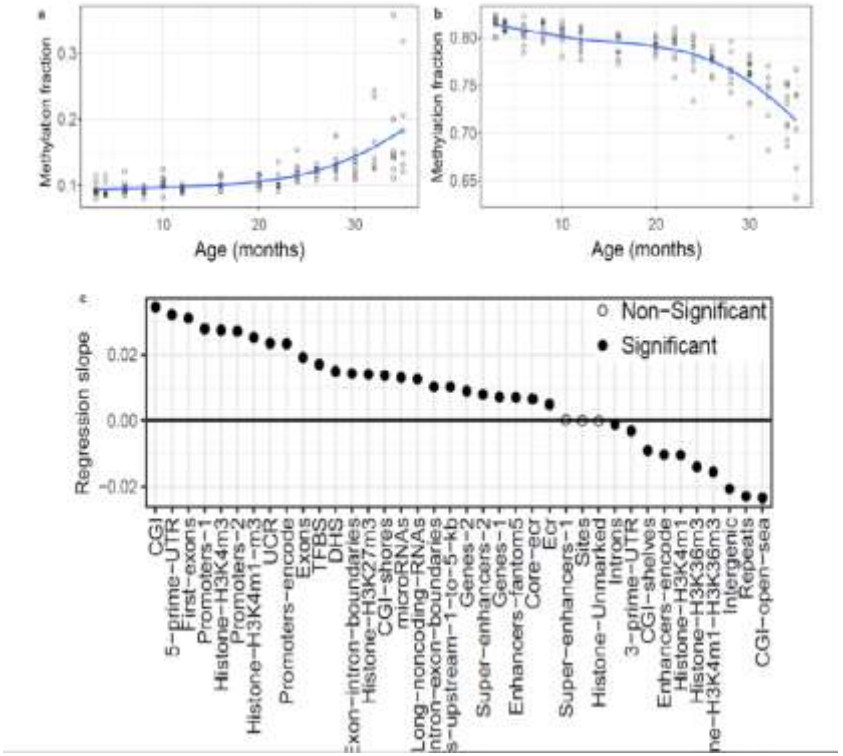




CpG Methylation, Epigenetic clock, reflect C.R., nutrition



Intrinsic age: Horvath multiple tissues.
Extrinsic Hannum, blood cell



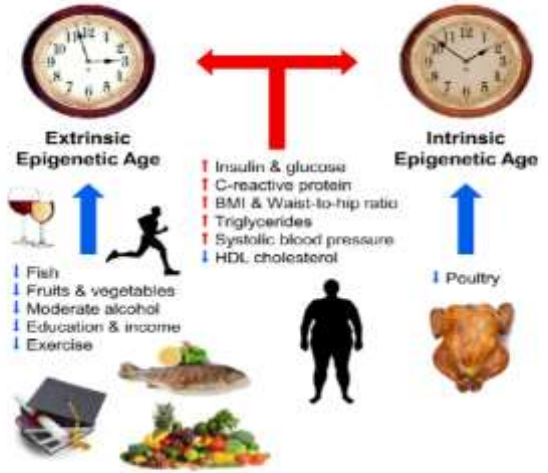


Figure 4. Pictorial summary of our main findings. The blue and red arrows depict anti-aging and pro-aging effects in blood respectively. The two clocks symbolize the extrinsic epigenetic clock (enhanced version of the Hannum estimate) and the intrinsic epigenetic clock (Horvath 2013) which are dependent and independent of blood cell counts, respectively.

www.aging-us.com AGING 2017, Vol. 9, No. 2
Research Paper

Epigenetic clock analysis of diet, exercise, education, and lifestyle factors

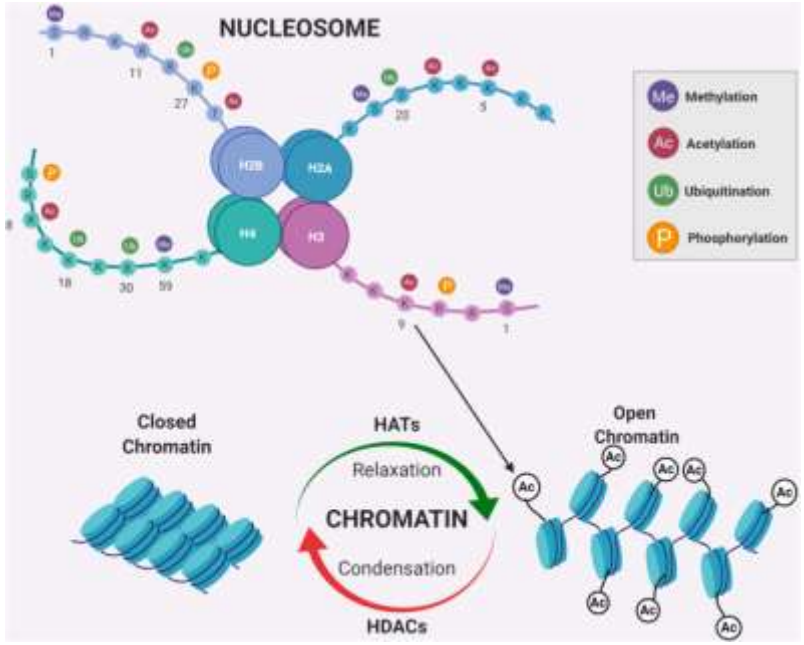
Austin Quach[1*], Morgan E. Levine[1*], Toshiko Tanaka[2*], Ake T. Lu[1], Brian H. Chen[1], Luigi Ferrucci[2], Beate Ritz[3,4], Stefania Bandinelli[5], Marian L. Neuhouser[6], Jeannette M. Beasley[7], Linda Snetselaar[8], Robert B. Wallace[9], Philip S. Tsao[10,11], Devin Absher[12], Themistocles L. Assimes[13], James D. Stewart[14], Yun Li[15,16], Lifang Hou[15,16], Andrea A. Baccarelli[17], Eric A. Whitsel[11,18], Steve Horvath[1,19]

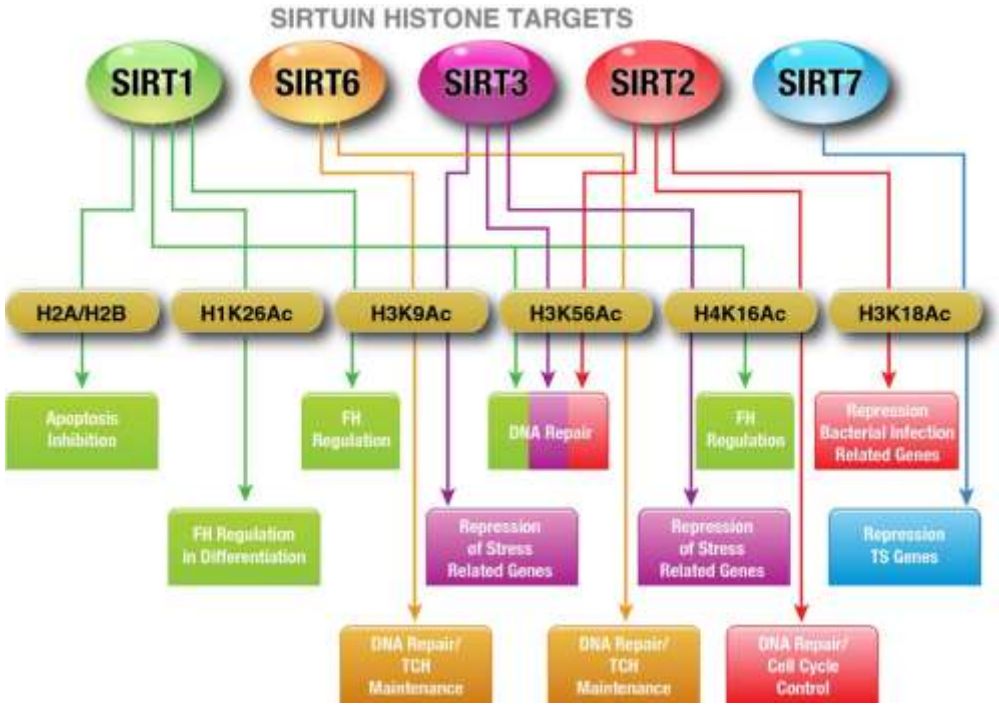
International Journal of Molecular Sciences
MDPI
Review

The Impact of Caloric Restriction on the Epigenetic Signatures of Aging

Noémie Gensous [1], Claudio Franceschi [2,3], Aurelia Santoro [3], Maddalena Milazzo [1], Paolo Garagnani [1,4,5,6,7,*] and Maria Giulia Bacalini [2]

Nutrition: central importance Epigenetic histone-mediated regulation: e.g. C.R. regulate sirts, (HDACs; do all benefit from a SIRT diet ?



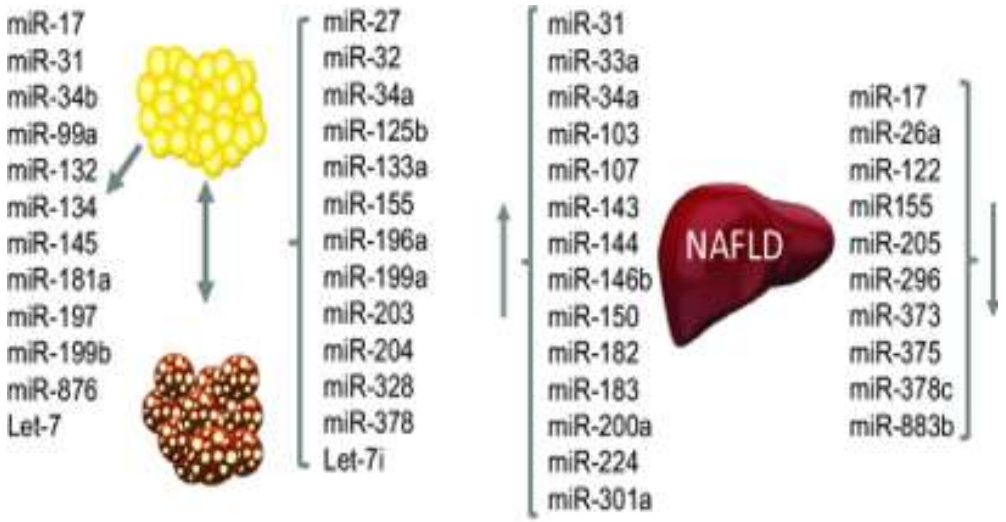


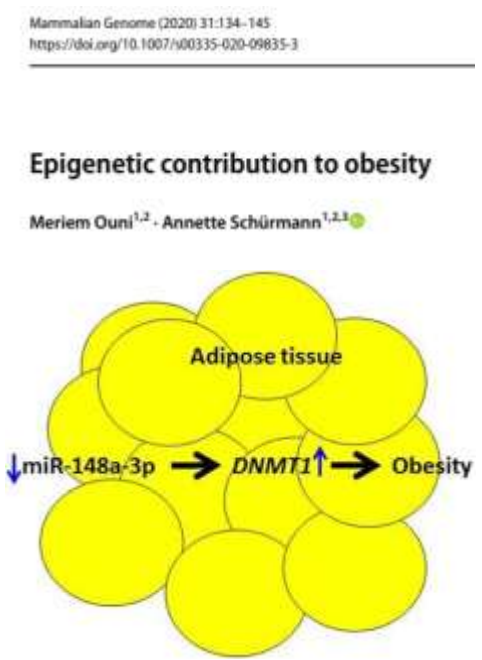
Epigenetic miRNAs: food borne and regulators and markers of metabolic mechanisms, phenotypes, disorders


PLOS ONE

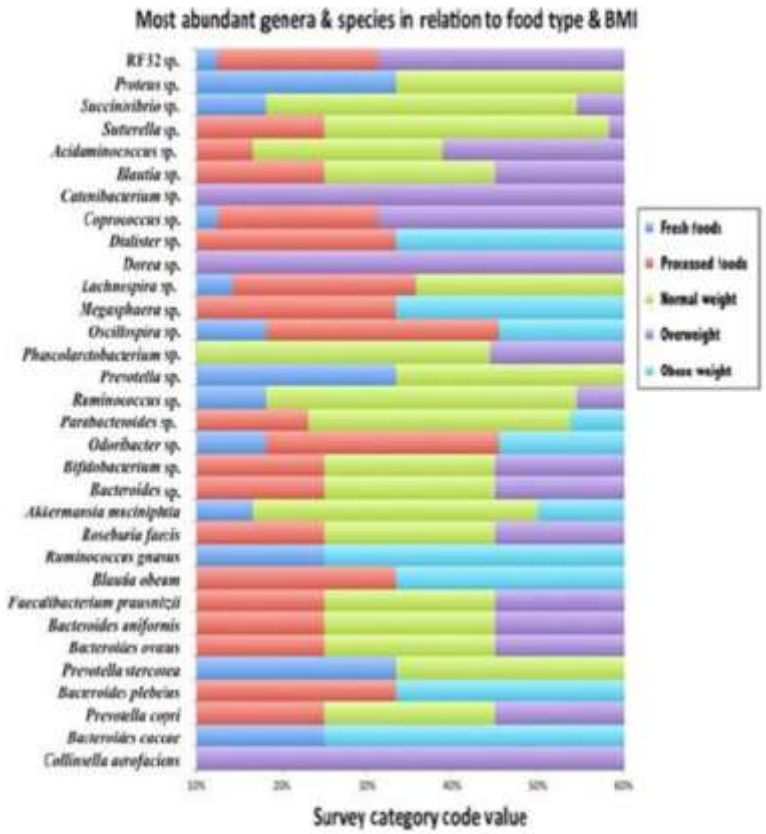
RESEARCH ARTICLE

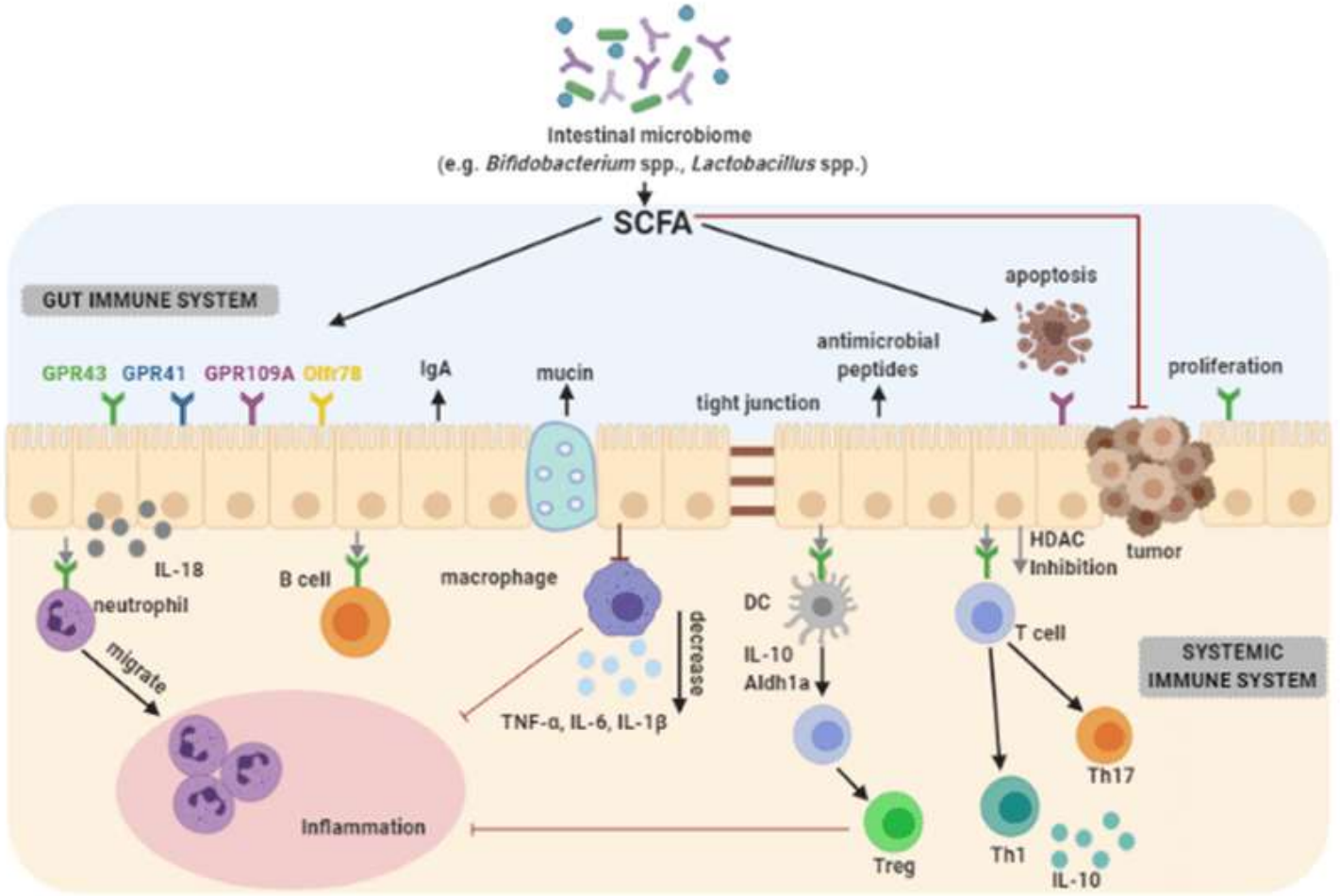
Dietary MicroRNA Database (DMD): An Archive Database and Analytic Tool for Food-Borne microRNAs





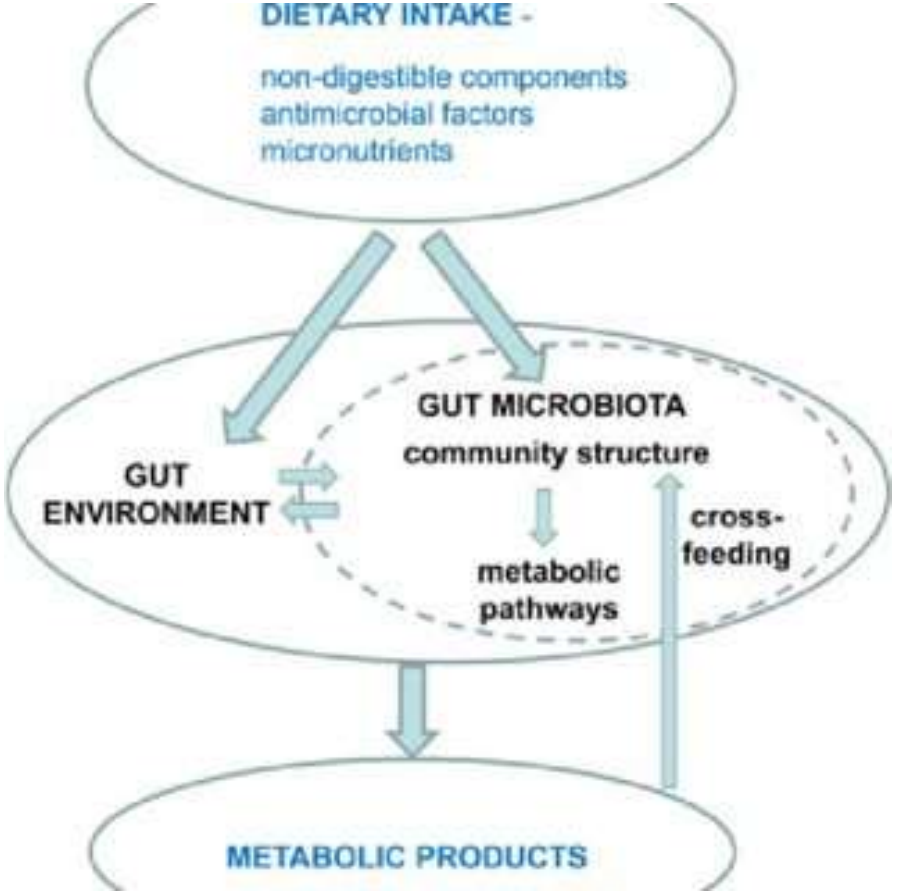
High Individual diversity of gut microbiota reflects nutrition and lifestyle , results in different expression of metabolites esp. SCFAs

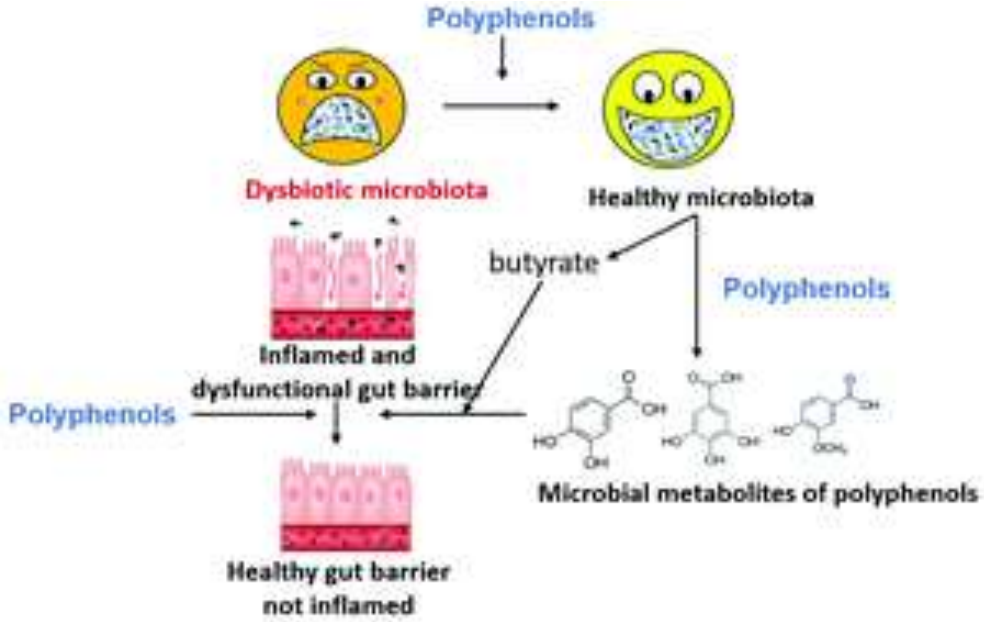




 Davis SC et al. / Microbiologyopen 2017

highly personal different responses of microbiota to diets, (crossfeedinG) and metabolisation of foods





Article | Open Access | Published: 12 March 2018

Understanding the prebiotic potential of different dietary fibers using an *in vitro* continuous adult fermentation model (PolyFermS)

Sophie A. Poeker, Anneleis Geirnaert, Laura Berchtold, Anna Greppi, Lukasz Krych, Robert E. Steinert, Tomas de Wouters & Christophe Lacroix

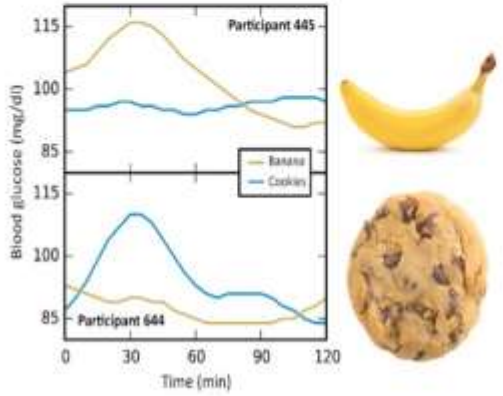
Scientific Reports 8, Article number: 4318 (2018) | Cite this article

H. Flint

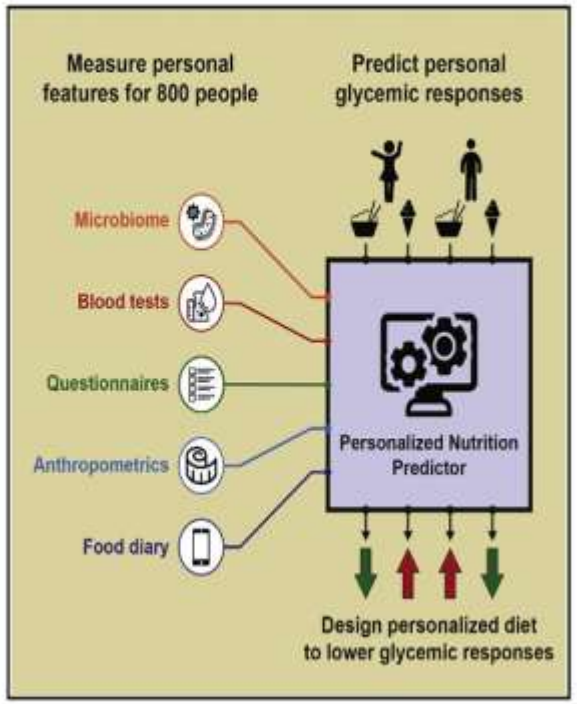
Correlation of microbiota structure with Glycemic responses used for algorithms for dietary advice

Beispiel - Personalized Nutrition by Prediction of Glycemic Responses
David Zeevi, 2016

- 800 Personen – jeder hat andere „post meal Glucose response“

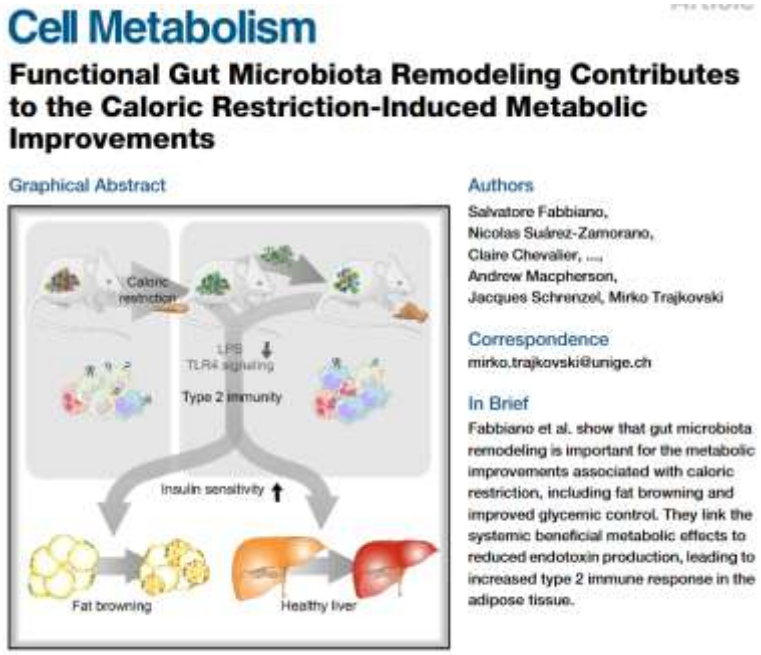


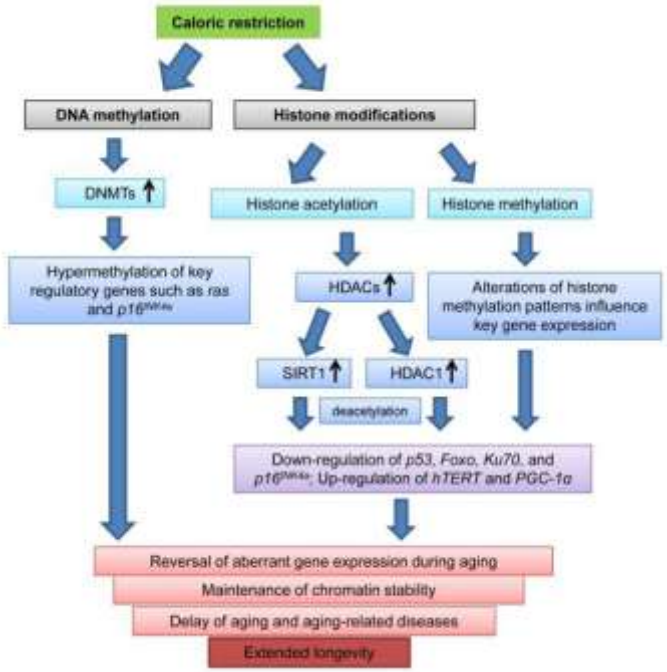
Mikrobiota Zusammensetzung beeinflusst Blutglucoselevel

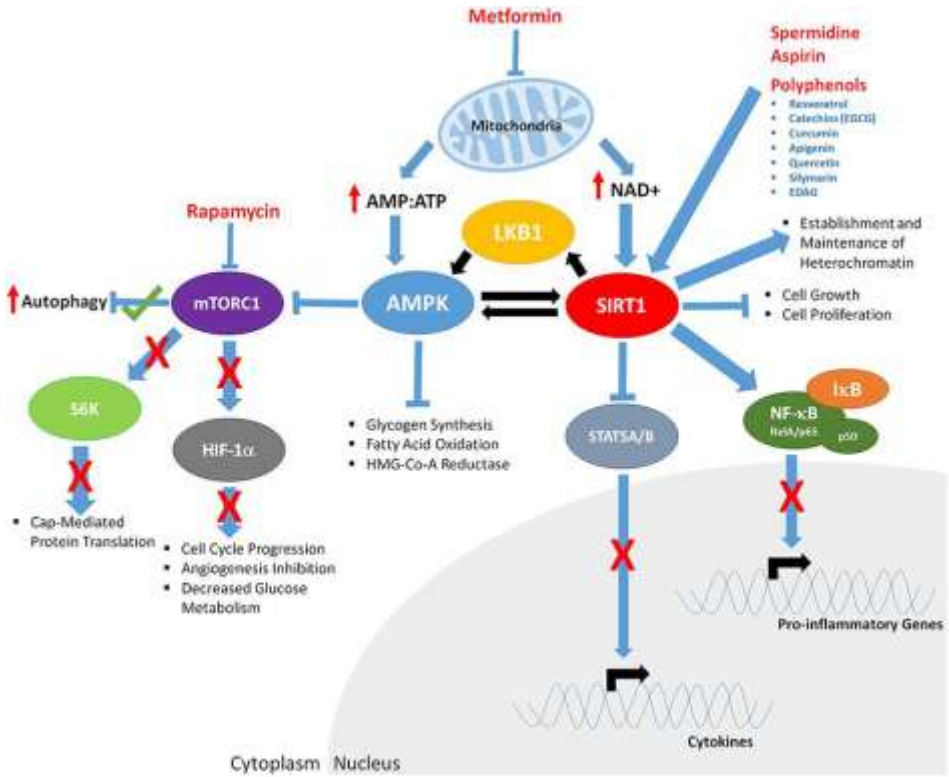


[Eran Elinav](#) and [Eran Segal](#), Weizmann Institute of monitoring the blood sugar, diets, and other traits of 800 people, [they built an algorithm](#) that can accurately predict how a person's blood-sugar levels will spike after eating any given meal.
They also used these personalized predictions to develop tailored dietary plans for keeping blood sugar in check.

So, Genetic and microbiota analysis for personal dietary plans, But of central importance are Interactions microbiota with epigenetic System; host gut interactions e.g. in C.R., Fasting (fasting Mimetics)







Personal different responses to nutriton affect aging, e.g. clock and other hallmarks of aging. this results in personal types of aging, ageotypes ?

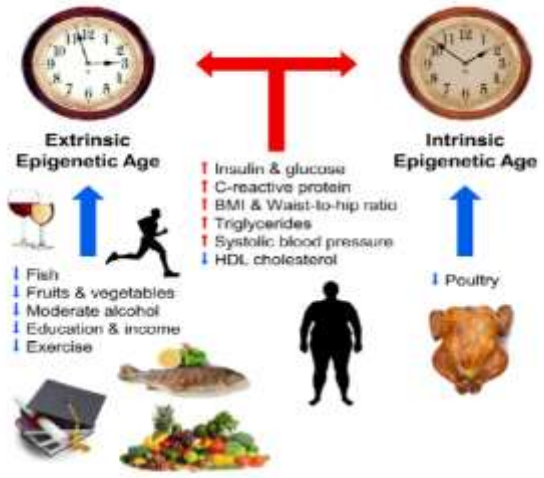
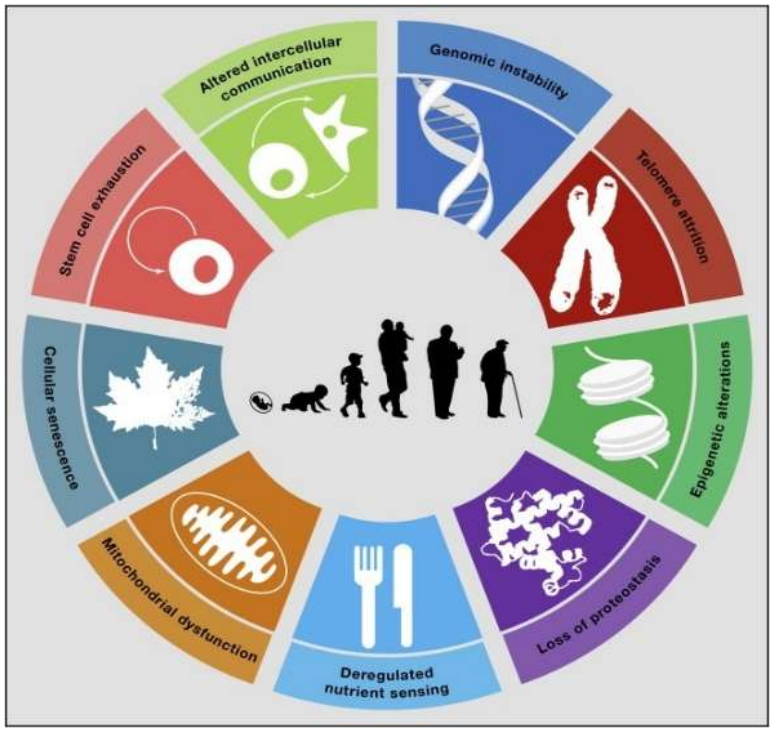


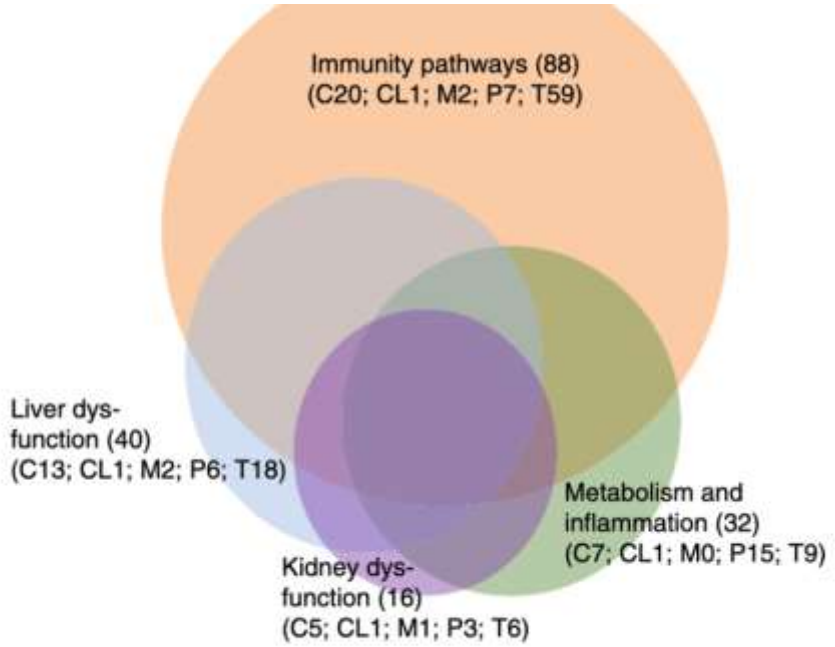
Figure 4. Pictorial summary of our main findings. The blue and red arrows depict anti-aging and pro-aging effects in blood respectively. The two clocks symbolize the extrinsic epigenetic clock (enhanced version of the Hannum estimate) and the intrinsic epigenetic clock (Horvath 2013) which are dependent and independent of blood cell counts, respectively.


nature medicine FOCUS | LETTERS

Personal aging markers and ageotypes revealed by deep longitudinal profiling

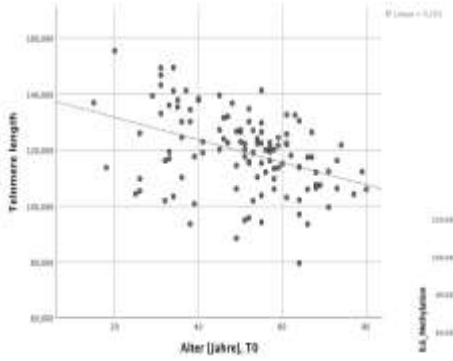
Sara Ahadi[1,4], Wenyu Zhou[1,4], Sophia Miryam Schüssler-Fiorenza Rose[1], M. Reza Sailani[1], Xinrin Contrepois[1], Monika Avina[1], Melanie Ashland[1], Anne Brunet[1] and Michael Snyder[1]*



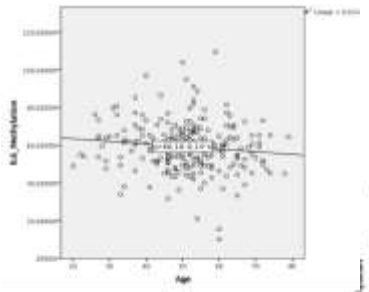


Venn diagram showing the number of analytes (C, cytokines; CL, clinical laboratory values; M, metabolites; P, proteins; T, transcripts) in each of the four ageotypes and the overlaps among them.

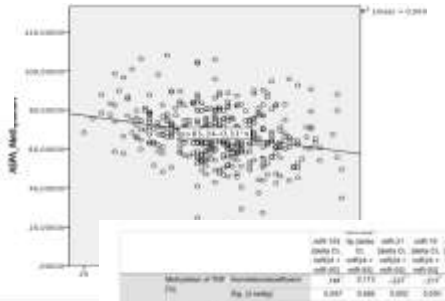
Faces of personal aging: correlations of age with telomers, CPG-methylation, inflammation, mirnas(n>500)



Correlation age with telomere-shortening

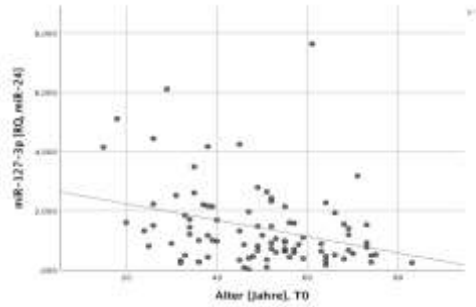


Correlation age with CPG methylation ASPA

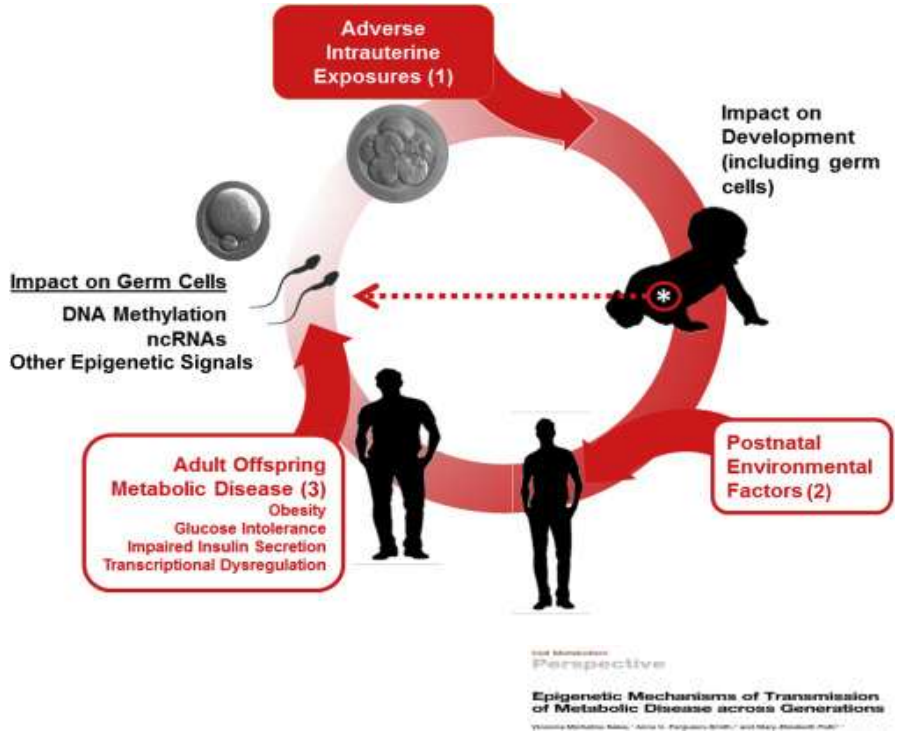


Correlation age with CPG methylation IL6

Correlation age with miRNA-127

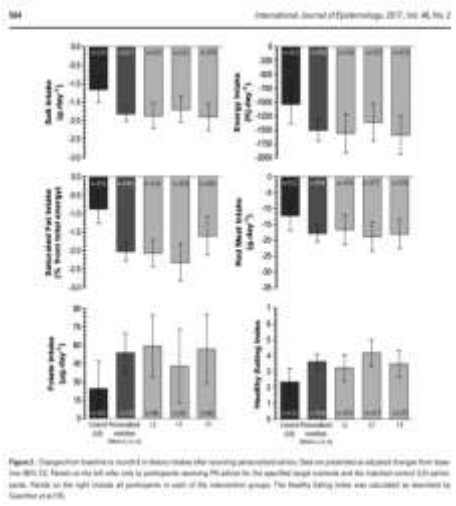


Conclusion: Complex diseases (Aging) can arise from (a mixture of) personal diverse causes, an argument in favor of personally specific interventions (e.g. metabolic disease)

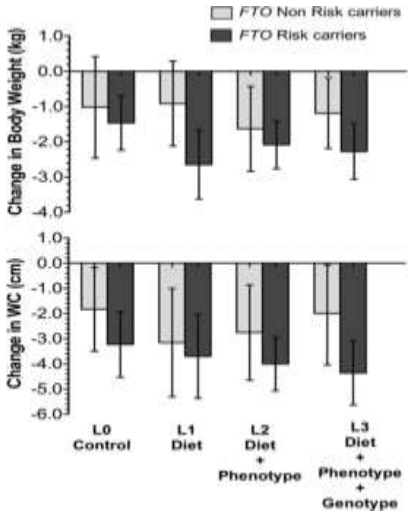


		Metabolic disorder
Hereditary SNPs Somatic mutatiions		Symptomatic treatment
Epigenetic (hereditary) or acuqired mismethylations, Histone modifocations or ncRNA structure		Causative treatment ? Epigenetic active additives? mTOR – Inhibitors ? Nutrition, Lifestyle
Delivery or accessed microbiota dysbiosis		Causative treatment ? pro-, pre, postbiotics? Nutrition, Lifestyle
Psycho- neuro- immune endocrine axis		

Consequences for Intervention: Flagship EU-Food4me study results prove „personal nutrition does better than on size fits all“, J. Mathers

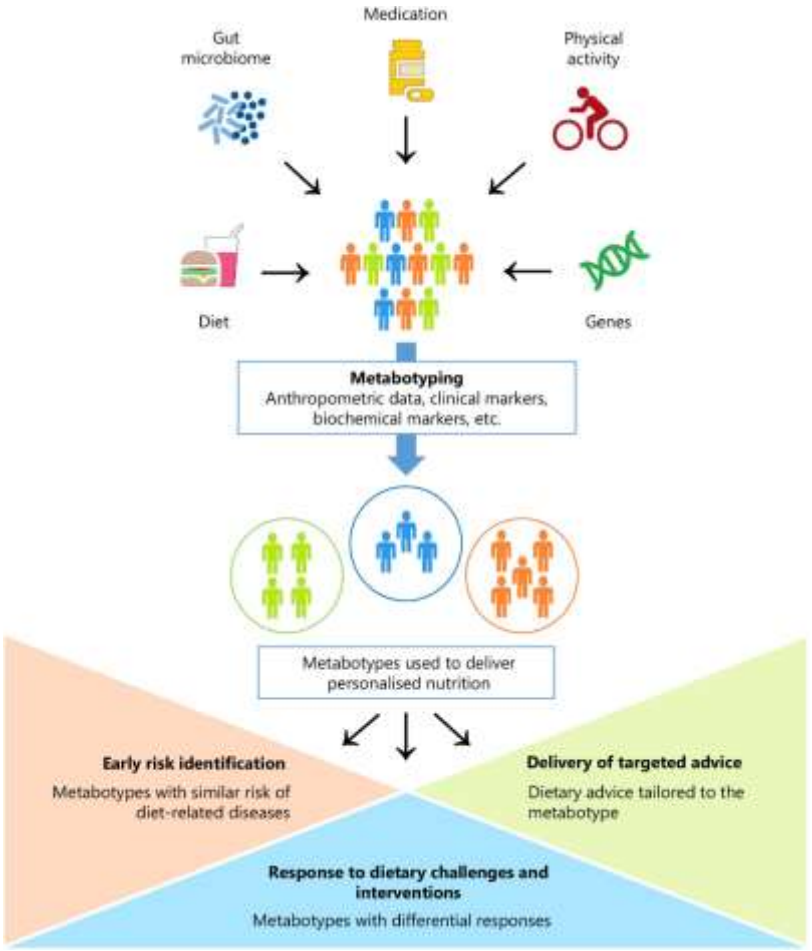


Changs of dietary intake
after personalised advice
Healthy eating index

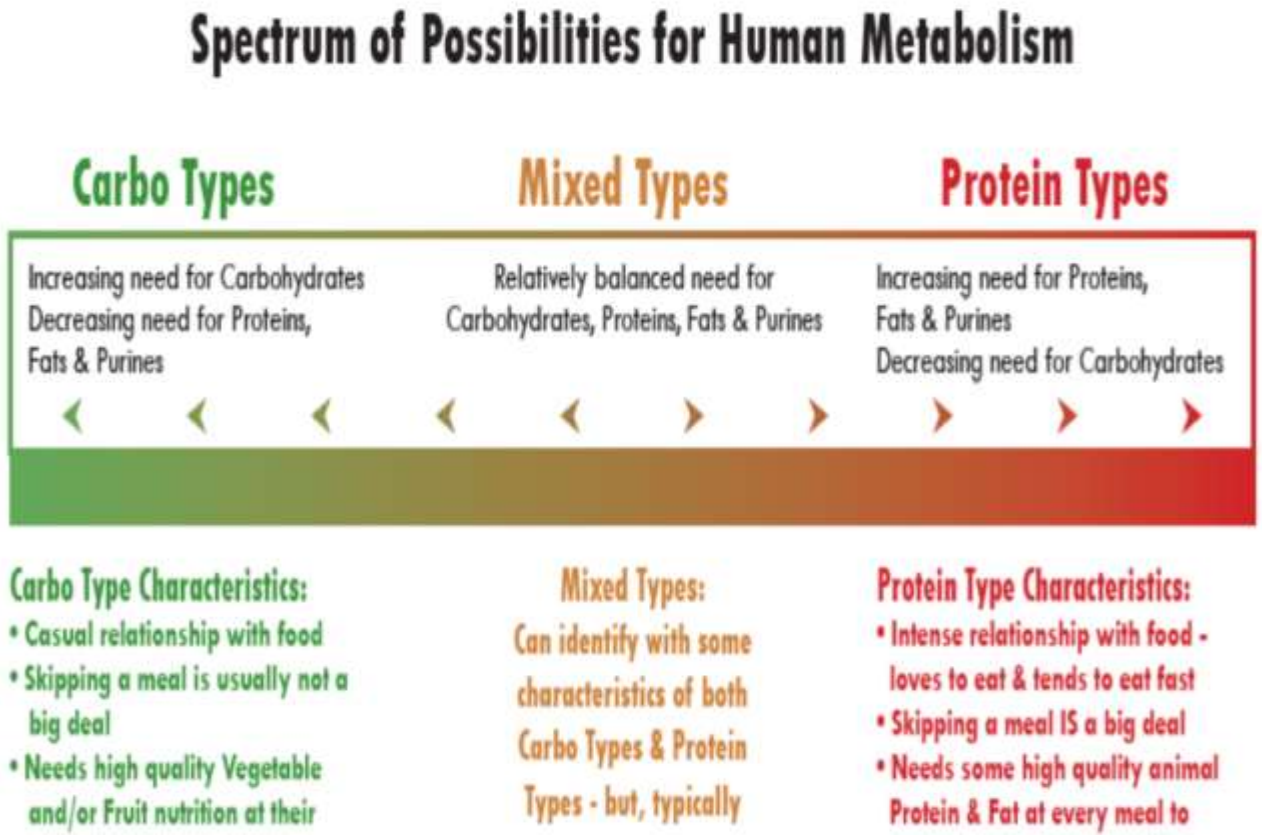


Changes in adiposity markers were greater in participants <u>who were informed</u> that they carried the *FTO* risk allele (level 3 AT/AA carriers) than in the nonpersonalized group

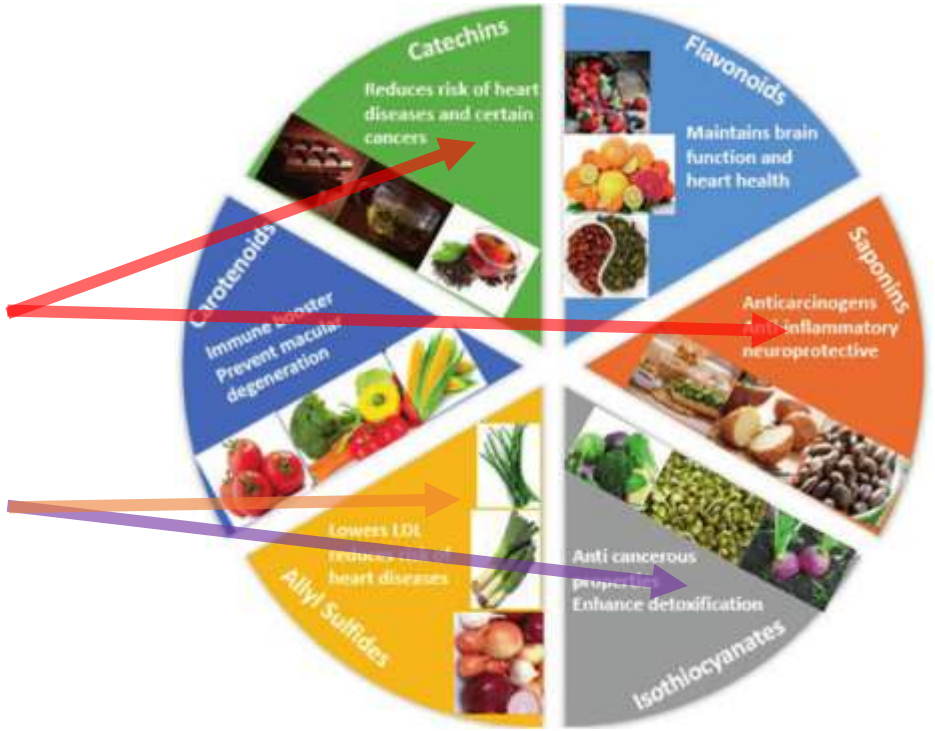
Definition of metabotypes from genetic-, microbiota-metabolomics based information, Metabotyping



Consequences of Metabotypes, diets next step trackers



Personalisation of additives for Prevention
Monitoring basic hallmarks of health/aging. Use of mixes of supplements, functional foods which address specific mechanisms „Achilles Fersen Concept“



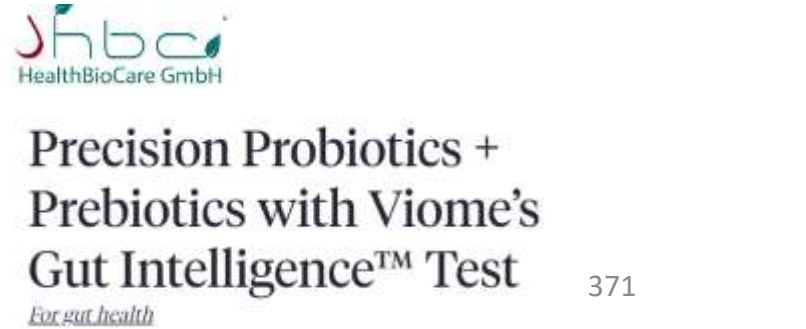

REVIEW
Epigenetic mechanisms in anti-cancer actions of bioactive food components – the implications in cancer prevention

FFHD
Mechanisms of selected functional foods against viral infections with a view on COVID-19: Mini review

REVIEW
Therapeutic perspectives of epigenetically active nutrients

Research Article
EGCG Prevents High Fat Diet-Induced Changes in Gut Microbiota, Decreases of DNA Strand Breaks, and Changes in Expression and DNA Methylation of *Dnmt1* and *MLH1* in C57BL/6J Male Mice

Gallic acid, a common dietary phenolic protects against high fat diet induced DNA damage



And what happens to the nutrition pyramide? But already the dietary reference values1992 US USDA-Pyramide, used an individualised approach, age, lifestyle (work)

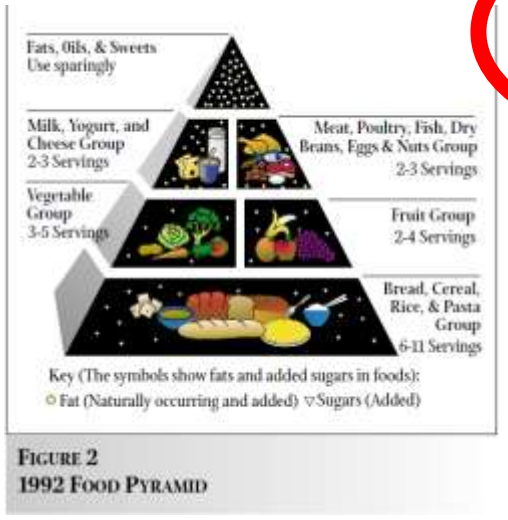


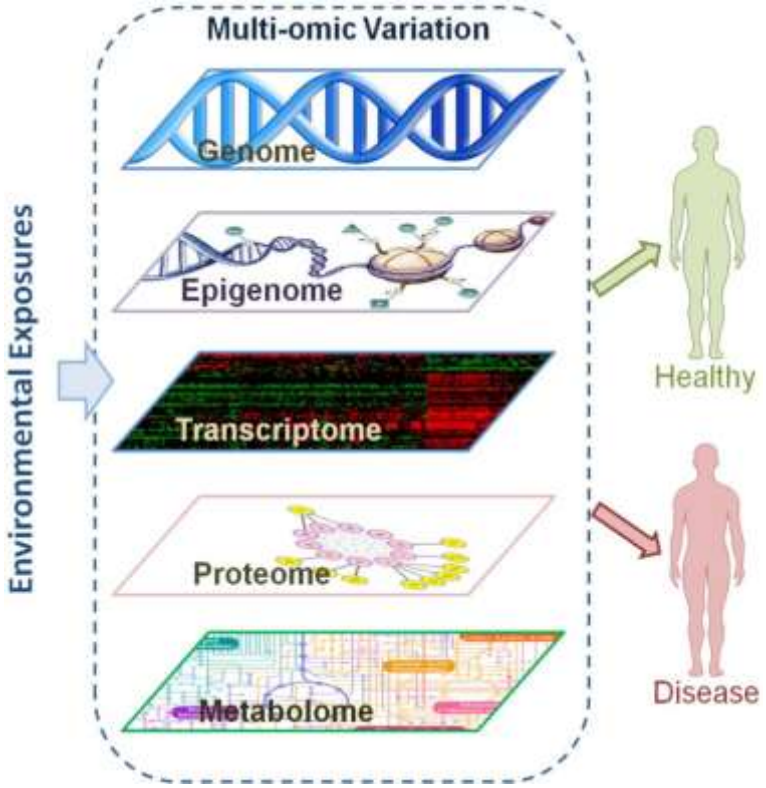
FIGURE 2
1992 FOOD PYRAMID

FIGURE 1
THE NEW FOOD PYRAMID ATTEMPTS TO IMPROVE HEALTH THROUGH MORE INDIVIDUALIZED APPROACH TO DIET

John Neustadt

Integrative Medicine 2005

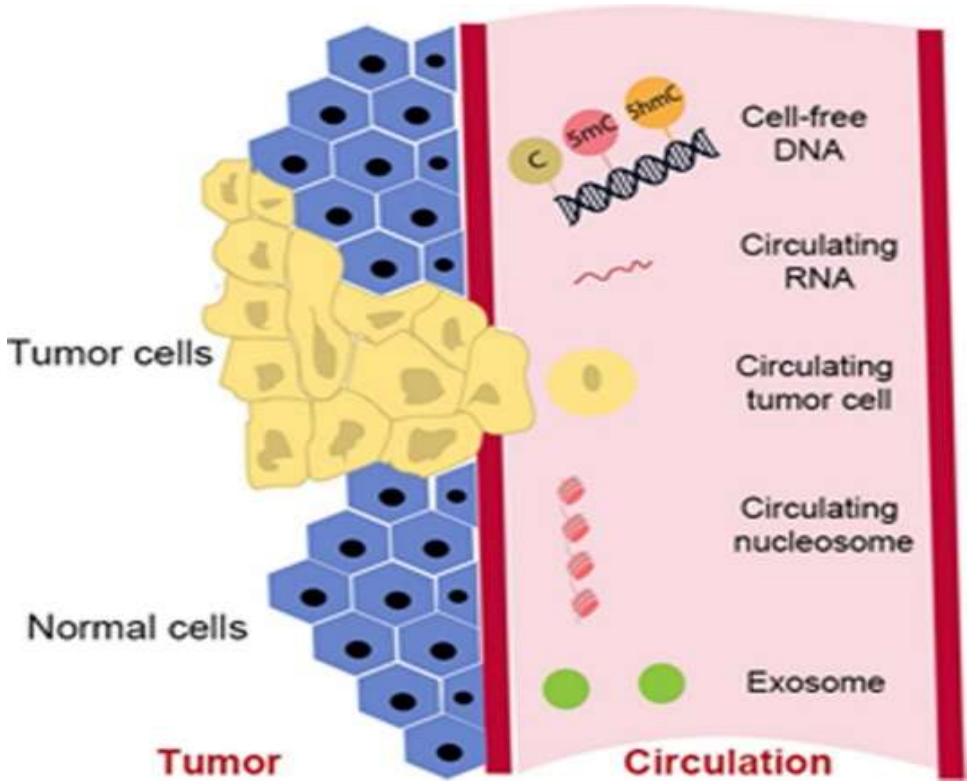
Importance of good Markers, Nutrition: following the way of personalised, prezision medicine, CFDNA) ?



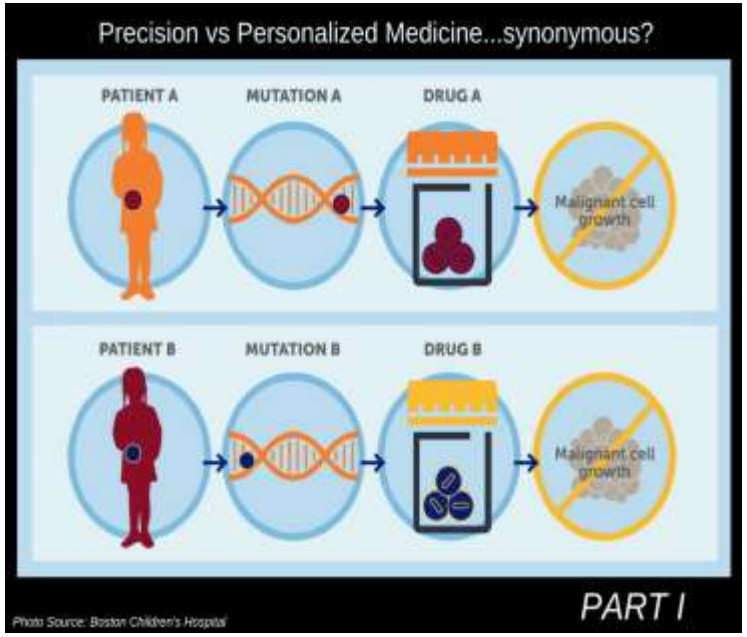
Epigenetic markers, quite stable, eg condens events over longer time spans

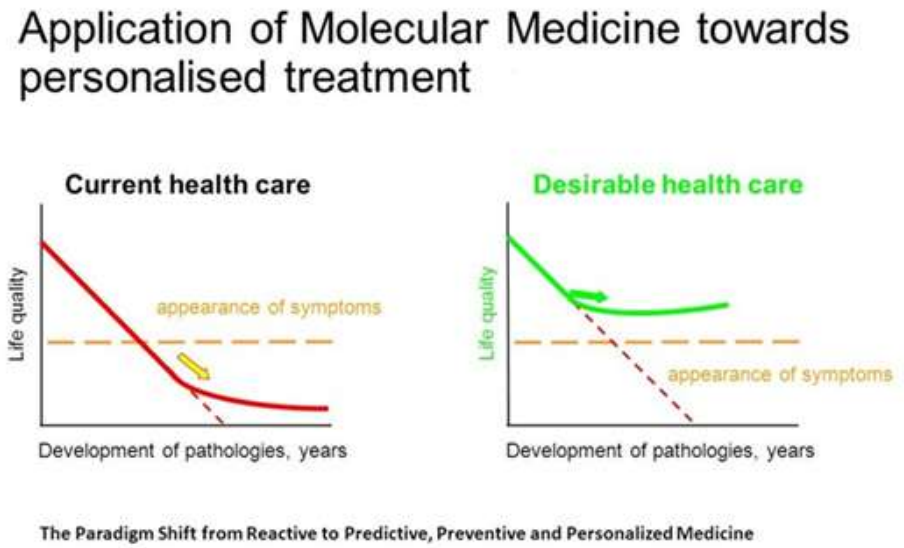
Metabolomic marker reflect more immediate

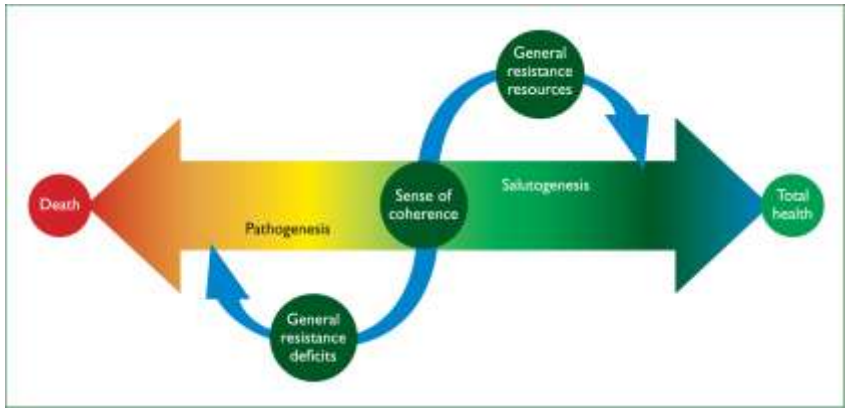

The Relevance of Epigenetic Biomarkers for Breast Cancer and Obesity for Personalised Treatment in Public Healthcare: A Systematic Review



Prevention, intervention, Salutogenesis personal or precision medicine, synonyme? personal or precision nutrition, synonyme?







Precision, personalised nutrition, where we are, where to go

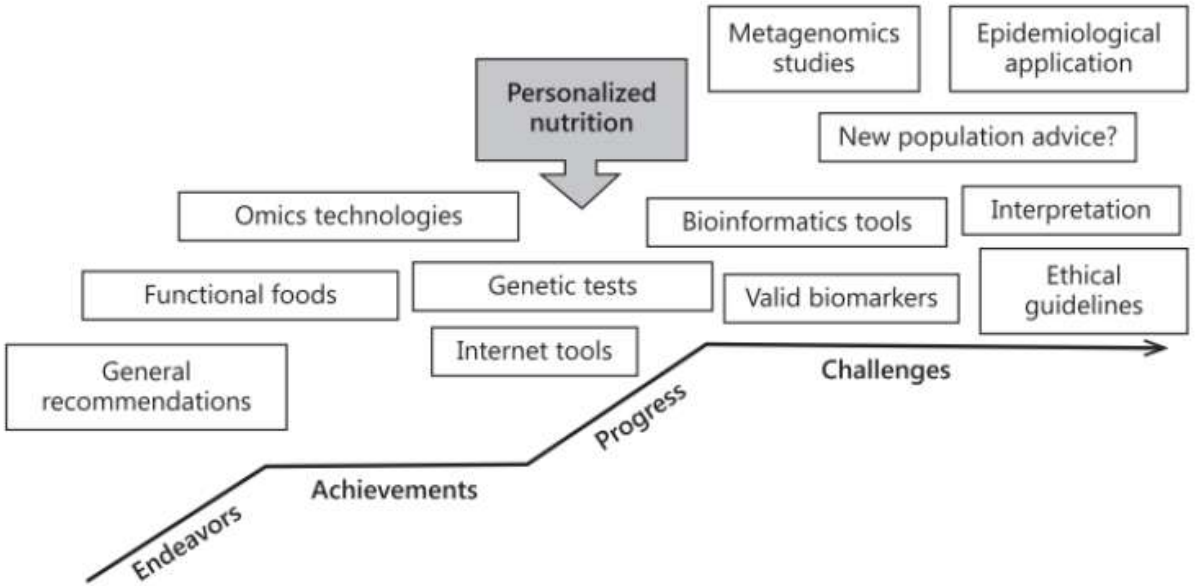


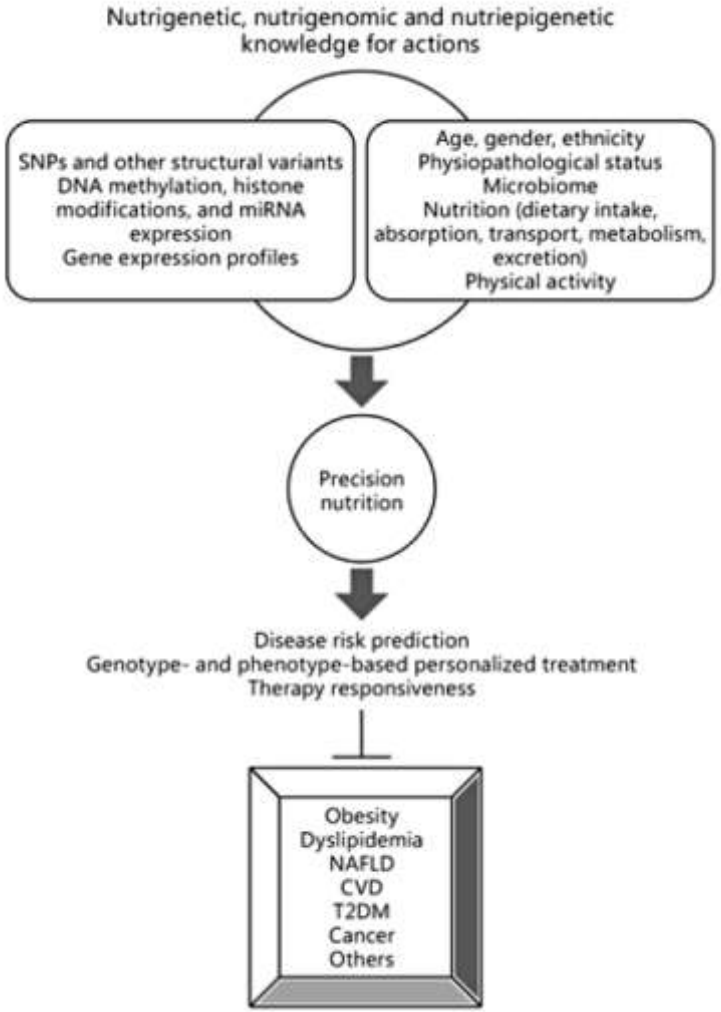
Fig. Achievements already made and challenges faced by personalised nutrition (Prasad et al., 2016)

Personalisierte Ernährung und Einteilung/ Klassifizierung von metabolischen Typen basierend auf genetischen, epigenetischen und mikrobiologischen Analysen

Personalized nutrition and classification of metabolic types based on genetics, epigenetics and gut microbiota

Stephanie Lilja, Diana Gessner, Christina Schnitzler, Nicola Stephanou-Rieser, Claudia Nichterl, Angelika Pointner, Elena Tomeva, Marlene Remely, Alexander Haslberger

Precision-, personalised nutrition, the way we may go

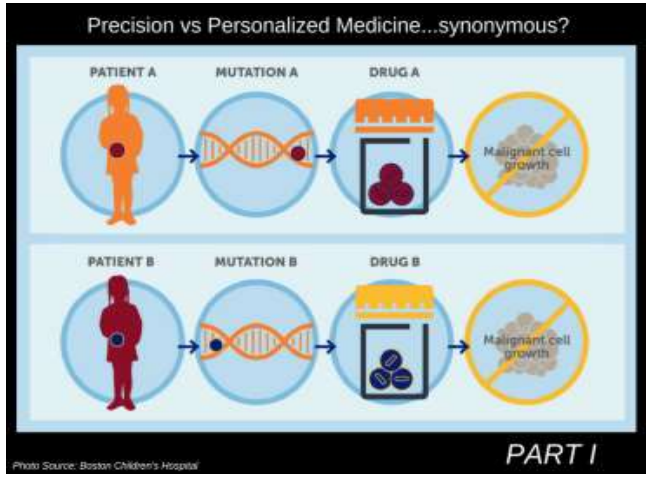


Mobile apps and wearable devices facilitate real-time assessment of dietary intake and provide feedback which can improve glycaemic control and diabetes management.

By integrating these technologies with big data analytics, precision nutrition has the potential to provide personalised nutrition guidance for more effective prevention and management of complex metabolic diseases

(D. D. Wang & Hu, 2018).

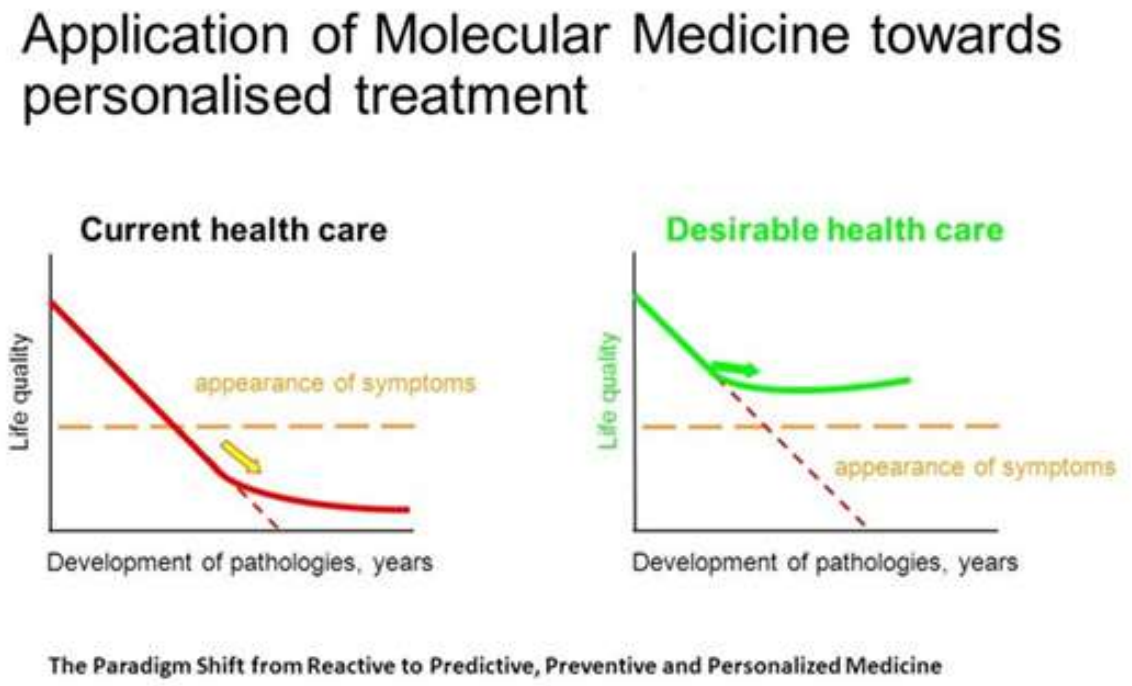
Prevention, intervention: personal precision medicine, personal precision nutrition



Objectives aging:

- longevity,?
- healthy life span ?
- age related complex diseases?

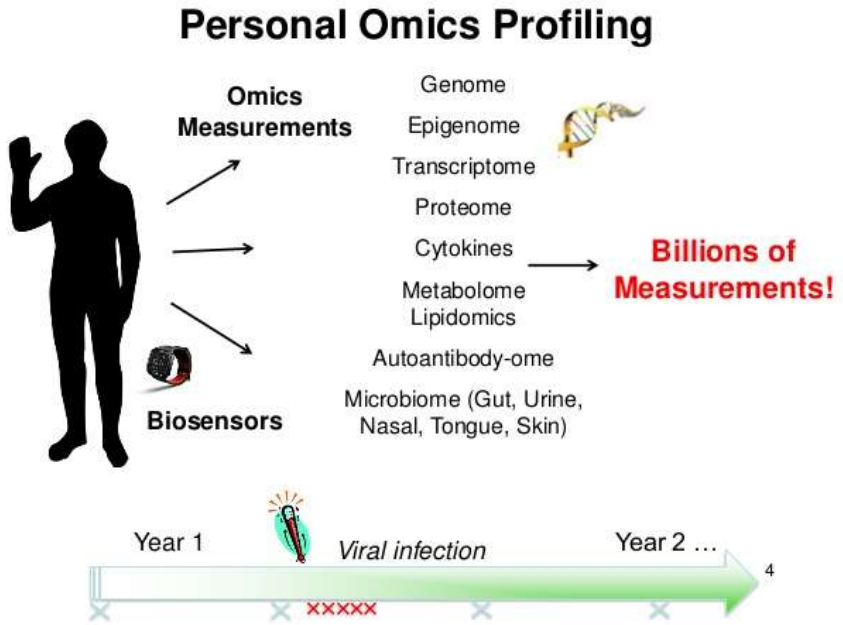
Analysis of molecular markers of different aging mechanisms and functional foods adressing the personal hazard may contribute to a personal, preventive health care, disease prevention, healthy aging



Objectives aging:

- longevity,
- healthy life span
- age related complex diseases?

Epigenetic and Salutogenesis : the bridge between scientific reductionism of markers and mechanisms and the need address the entire person ?



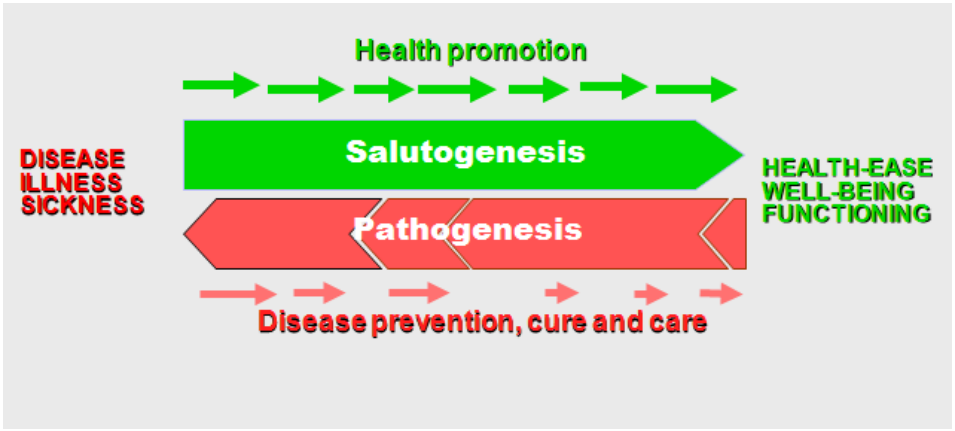
Epigenetics – bridging the gap between nature and nurture

Save 40% on an annual subscription to *BBC Science Focus Magazine*

Epigenetic research is uncovering the ways in which diet, lifestyle and the environment can affect your genes. As Nessa Carey discovers, this may change the face of evolution as we know it…

By Nessa Carey

12th August, 2015 at 14:00



Wer bestrebt ist, die Wahrheit vollkommen in sich zu erkennen, muss den Balken des Stolzes, der das Licht vom Auge abhält, entfernen und in seinem Herzen Stufen bereiten, durch die er sich in sich selbst erforscht.

www.my-personal.health