Novel Foods
Haslberger WS 2025

- 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

1

Materials

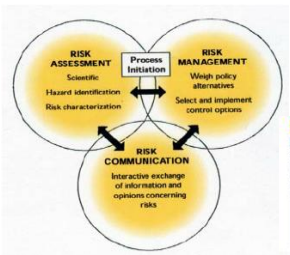
2

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.

3

WHO , UN, Risk Assessment



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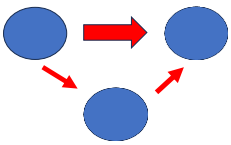
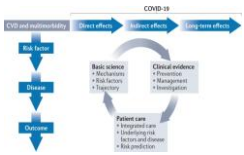
Direct, indirect risk, (long term) Epidemiologie





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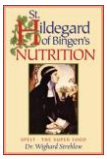
Nutrition, Foods , Health

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"**



6

Foods, functions, claims

7

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

7

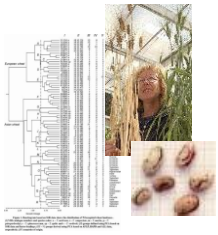
8

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,



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9

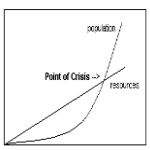
GREEN Revolution

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)

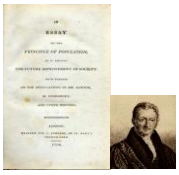
13

10

T. Malthus: 1766- 1834
Crisis in food production



Malthus' Basic Theory



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Models for population growth and food security:

Pessimistic or Alarmist Theory

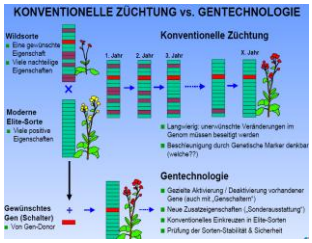
Malthus - 19th century, Coale & Hoover (1958),
Paul Ehrlich (Population Bomb),
Meadows (Limits to Growth) – 1960s and 1970s.
Focus on population policy & fixed, non-renewable resources.

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

Neutralist or Revisionist Theory

12

Pflanzenzüchtung
Breeding, yield, time for development



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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.

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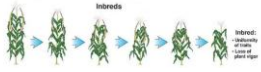
Hybridzüchtung, Heterosis

- 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



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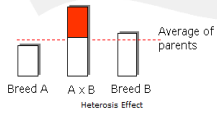
Hybrid: Heterosis effect

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.



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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	Aibvar	sodium azide
	Lewis	thermal neutrons
oats	Asamo-X	X-rays
grapefruit	Rio Red	thermal neutrons
	Star Ruby	thermal neutrons
bumuda 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
flax	Prairie Pebbe	thermal neutrons
St. Augustine grass	TXSA 8282	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.

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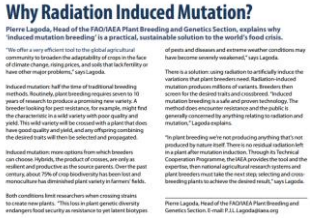
IAEA



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

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Breeding: Irradiation

Breeding: Irradiation

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

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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 122, 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, *Nietropika*. Contact Mrs Iris Human at E-mail: iris@itsc.agric.za to order a copy of the article.

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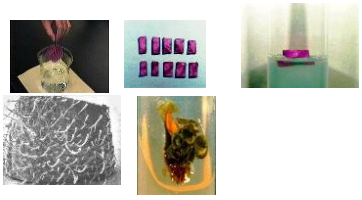
Tissue culture , Clones ?



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Somaclonal variation

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

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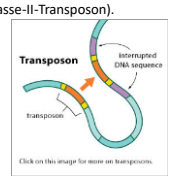
Breeding using transposons

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).



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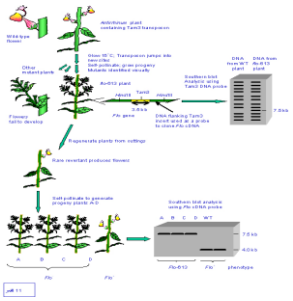

Transposon tagging

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

75

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Molecular marker directed breeding

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25

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

Allen Kelley/Ron Lee/Simon Kuznets/Nat'l Academy of Sciences 1986 Report – mid 1980s to the present. Focus on longer-term, policy feedbacks, mixed impacts, renewable resources & property rights.

Population Matters by Nancy Birdsall et al – 1990s (surveys confirm overall negative impact of population growth on per capita output growth across a large # of countries)

26

Landuse and property

conservation : expolitation

use : property

27

Nature and property

Science 13 December 1968:
Vol. 162. no. 3859, pp. 1243 – 1248

Articles
The Tragedy of the Commons

Garrett Hardin
professor of biology, University of California, Santa Barbara.

When a resource is held "in common," with many people having "ownership" and access to it, Hardin reasoned, a self-interested "rational" actor will decide to increase his or her exploitation of the resource since he or she receives the full benefit of the increase, but the costs are spread among all users.

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DERSTANDARD

Sich treu bleiben.

Friedrich August von Hayek: Ein Leben für den freien Markt

Eine exzellent recherchierte neue Biografie widmet sich den turbulenten ersten fünf Jahrzehnten im Werdegang des vielseitigen österreichischen Gelehrten


BUSINESS LEADERS + RICH & POWERFUL

Who Was Friedrich Hayek? What Was His Economic Theory?

By WILL KENTON Updated December 06, 2022
Reviewed by THOMAS J. CATALANO

Friedrich Hayek was a famous economist, well-known for his numerous contributions to the field of economics and political philosophy. Hayek's approach mostly stems from the Austrian school of economics and emphasizes the limited nature of knowledge. He is particularly famous for his defense of free-market capitalism and is remembered as one of the greatest critics of the socialist consensus.

Am 2. August 1940 landete der österreichische Nationalökonom Ludwig Edler von Mises (1881 bis 1973) in New York. „Die Welt war in Aufruhr, der Krieg wütete, als wir von Europa Abschied nahmen", schreibt seine Frau Margit 1978 im Vorwort zu den Erinnerungen ihres Mannes. Als jüdischer Intellektueller, der zu allem Überfluss auch noch den Kapitalismus rechtfertigte, war für von Mises an österreichischen Universitäten kein Platz.


Die Tea Party begann im Kaffeehaus

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What Is Keynesian Economics?

FINANCE & DEVELOPMENT, September 2014, Vol. 51, No. 3

Sarwat Jahan, Ahmed Saber Mahmud, and Chris Papageorgiou

PDF version

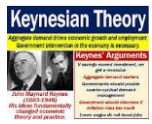
The central tenet of this school of thought is that government intervention can stabilize the economy.

Just how important is money? Few would deny that it plays a key role in the economy.

During the Great Depression of the 1930s, existing economic theory was unable either to explain the causes of the severe worldwide economic collapse or to provide an adequate public policy solution to jump-start production and employment.

British economist John Maynard Keynes spearheaded a revolution in economic thinking that overturned the then-prevailing idea that free markets would automatically provide full employment—that is, that everyone who wanted a job would have one as long as workers were flexible in their wage demands (see box). The main plank of Keynes's theory, which has come to bear his name, is the assertion that aggregate demand—measured as the sum of spending by households, businesses, and the government—is the most important driving force in an economy. Keynes further asserted that free markets have no self-balancing mechanisms that lead to full employment. Keynesian economists justify government intervention through public policies that aim to achieve full employment and price stability.

Keynesians believe that, because prices are somewhat rigid, fluctuations in any component of spending—consumption, investment, or government expenditures—cause output to change. If government spending increases, for example, and all other spending components remain constant, then output will increase.



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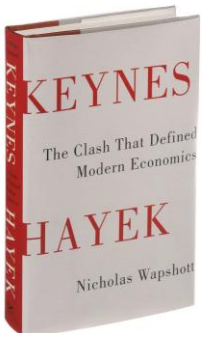

As Keynes stood to the left, so Mises stood to the right—and for the right. While Keynes would arm the government with extraordinary peacetime powers—oblivious to the Actonian principle that power corrupts—
Mises called for limited, non-interventionistic government.

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Nature and property. Public goods

Industrial and Corporate Change
Pp. 131-159

OSTROM, E. © 1995 Oxford University Press

research-article

Self-organization and Social Capital
(building public goods)

ELINOR OSTROM

(Workshop in Political Theory and Policy Analysis, Indiana University Bloomington, IN 47408–3895, USA)

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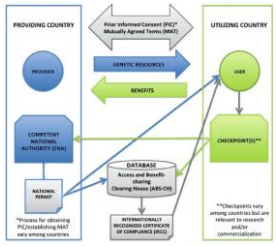
Benefit sharing, genetic ressources



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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.

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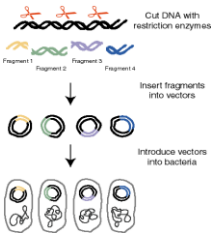
DNA cloning:



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.

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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.

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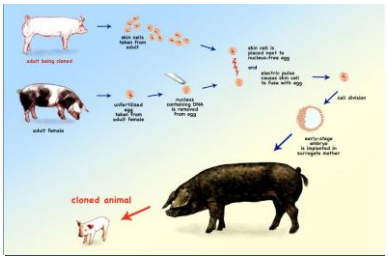
Reproductive Cloning



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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.

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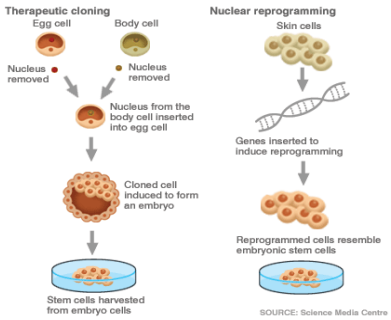

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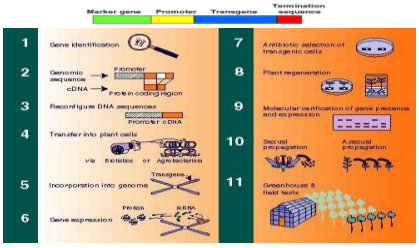
Horticultural cloning

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.

40

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



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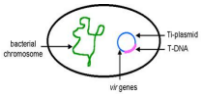
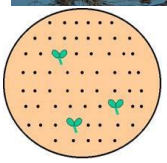
Agrobact. tumefaciens





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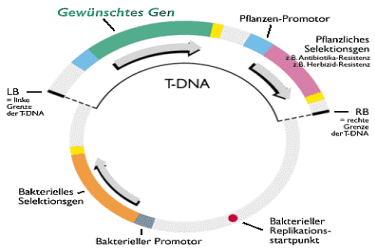

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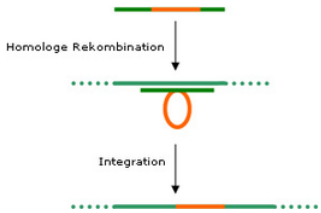
Homologic recombination



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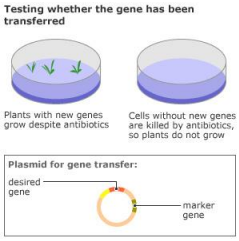
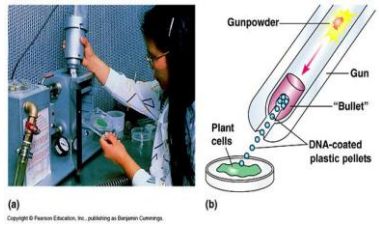
Antibiotic resistance marker gene



45

Gene gun



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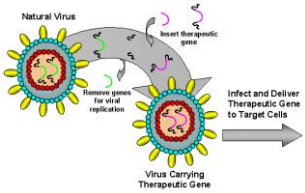
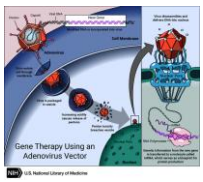
Gene transfer with viruses





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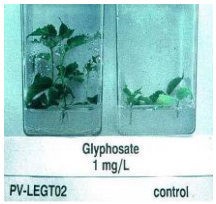
Main GMOs, Herbicide tolerance, glyphosate



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Herbicide Resistant Soybean

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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)

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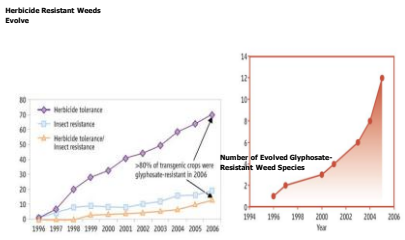
Old and new Problems: Resistance



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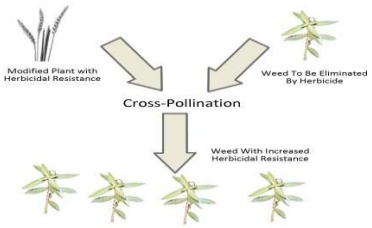
Herbizide resistance, gene transfer



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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

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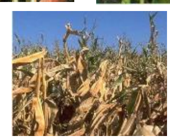
Insect resistance, BT maize







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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

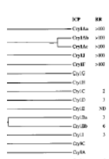

FIG. 1. Amino acid sequence similarity of domain II of *B. thuringiensis* toxins and resistance ratios (RR) of diamondback moth larvae. The dendrogram was

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Roundup ready, Monsanto

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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)**

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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)

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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

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Disease Resistance, viruses

Genetically engineered papaya resistant papaya ringspot virus

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

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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)

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GM Salmon

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

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

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- 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

BELPOND-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.

63

GMO tobacco, expression of human proteins in plants

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GMOs in development:
CLAIMED BREEDING OBJECTIVES

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CLAIMED BREEDING OBJECTIVES

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09.12.2008

Claimed breeding objectives

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BREEDING OBJECTIVES

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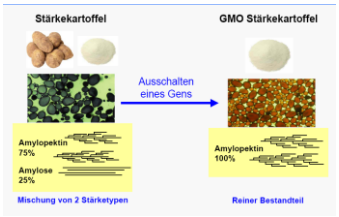
Breeding objectives



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GMO Trees

GENETICALLY MODIFIED TREES: PRODUCTION, PROPERTIES, AND POTENTIAL

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.

70

GM FLowers

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

Source: DailyTech • October 30, 2009

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.

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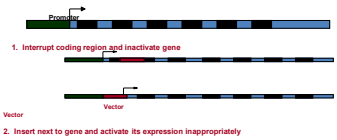
Safety: Random integration, Insertional mutagenesis



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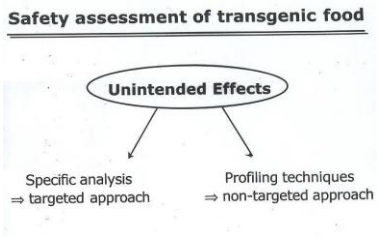

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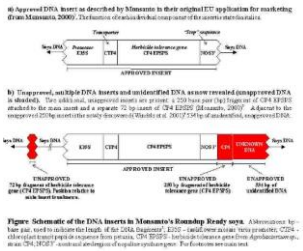

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Toxicology Asessment: Difficulties Animal Feeding Studies
Whole Foods

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

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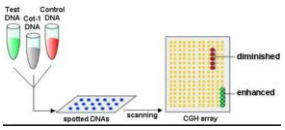
Detection of unintended effects in vitro, in vivo



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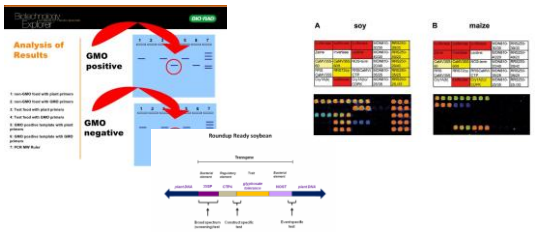
GMO tests: PCR, primers, areas, array



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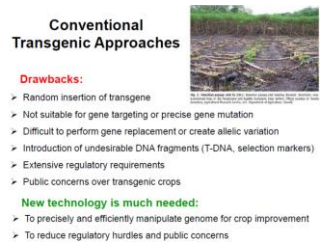
New Objectives for gene transfer



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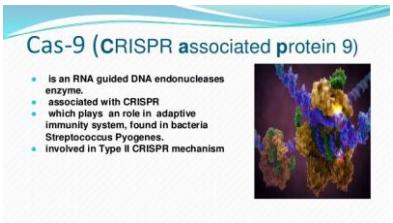
Gene editing



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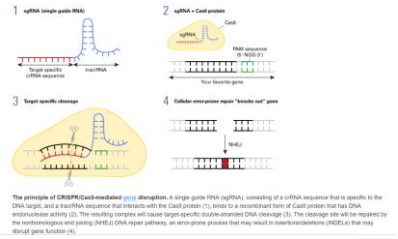

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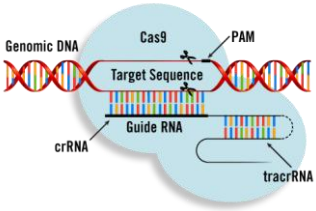
CRISPR/CAS9



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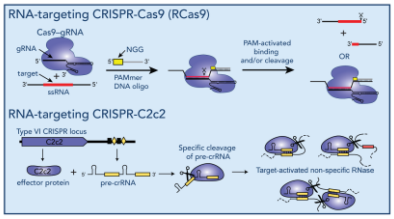
Targeting RNA



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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

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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
Tsuchiro-mochi	Yes	Japonica	I	R	H	D	A
Tetep	Yes	Indica	I	R	H	D	A
C101A51	No	Indica	I	R	H	D	S
Toyosatsu	No	Japonica	S	S	Q	V	S

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

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Video gene editing

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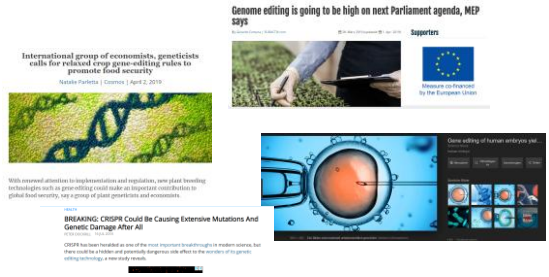

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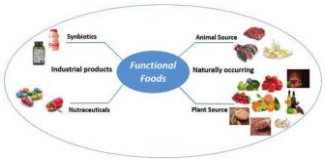
Novel food, functional food, pro-, pre-, syn-, postbiotics



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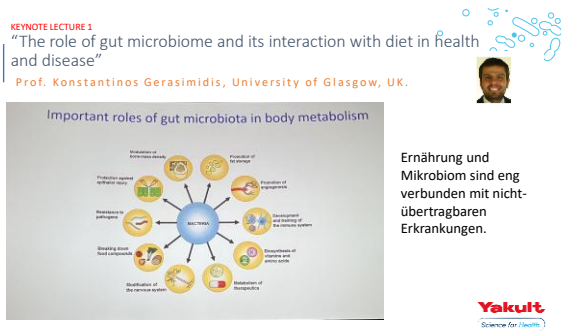

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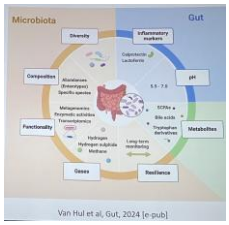
KEYNOTE LECTURE 1

"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

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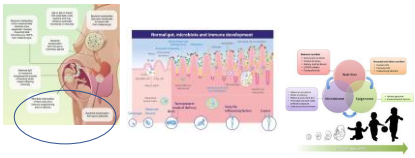
Development of microbiota, I.s., and epigenetic system, imprinting



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

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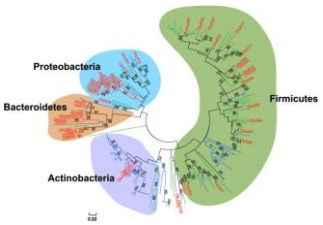
Structure microbiota



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

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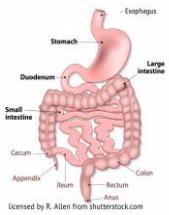
GI Microbiota

HUMAN GASTROINTESTINAL TRACT

Stomach & Duodenum
10^1– 10^3 CFU/mL
Helicobacter
Streptococcus

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



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

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"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

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Variation in microbiota structure is high

Despite high variation, GI microbiota depend on :

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

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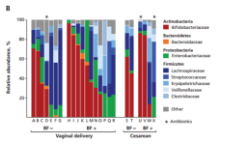
Ways of delivery and microbiota: a long lasting difference

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*.



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

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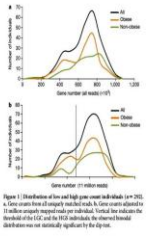
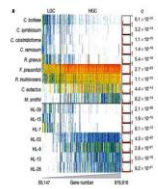
GI microbiota: Diversity of groups and functions important for health





[Le Chatelier E. et al., 2013] MetaHITConsortium

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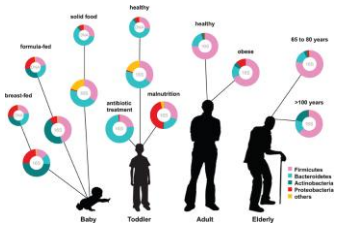
Aging and Microbiota



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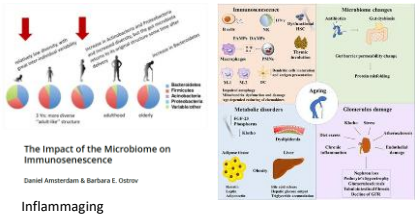
Interactions Microbiota diversity - I.S.- epigenetic system in senescence



Inflammaging

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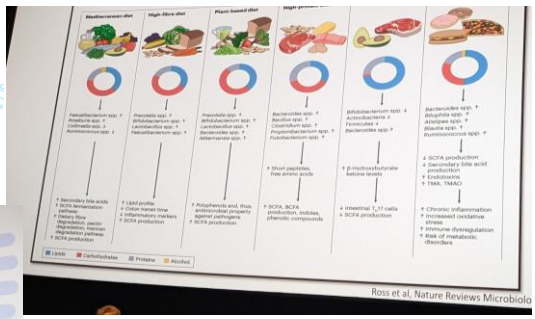

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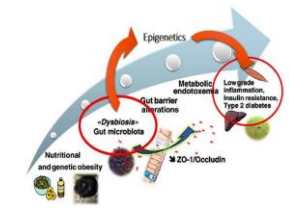
Bacterial cell wall components and Inflammation: dysbiosis, LPS and gut permeability; obesity as a model



(Cani et al, 2011)

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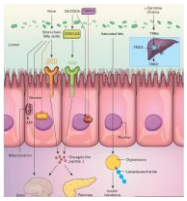
Endotoxins, saturated fats/ chylomicrons trigger inflammation, insulin resistance;
SCFAs may trigger GLP1 activation

GLP1: incretin improves DMII and obesity



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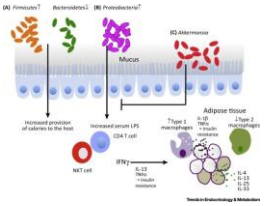
Obesity: Firmicutes: Bacteroidetes;
Akkermansia and the cell wall



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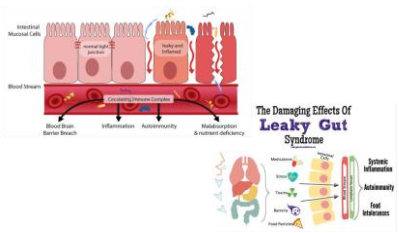
leaky gut: a major health problem



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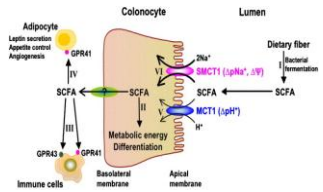
Microbiota metabolites: SCFAs bind to
G-Protein-Receptors GPR 41/43 (FFARs)



Anti-inflammatory;
Inhibition of NFκB

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

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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)

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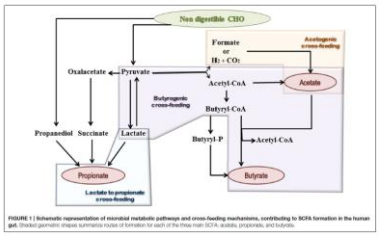
Pathways and cross feeding for SCFAs/ Butyrate



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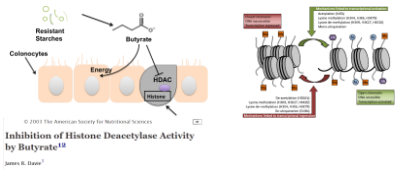
Butyrate and epigenetic histone modulation



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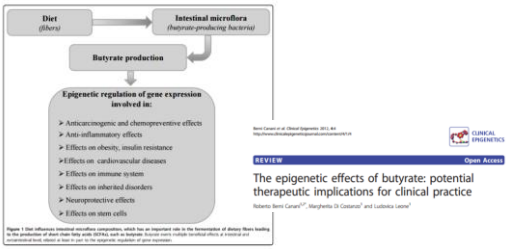
Butyrate and epigenetics



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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, ARH460 (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-thymidine 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; HDAC), 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, trichostatin A (histone hyperacetylation inhibitor).

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

Karen S Bishop[1], Huaiwen Xu[2] and Gareth Marlow[1]

[1]Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University

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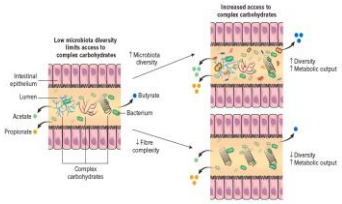
Diet dictates the production of SCFAs, diversity of the microbiota, many types of complex carbs



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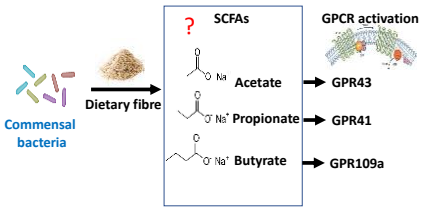
Mechanism of action of fibre: Short-chain fatty acids (SCFAs)?

- SCFAs are major metabolites produced by the microbiota



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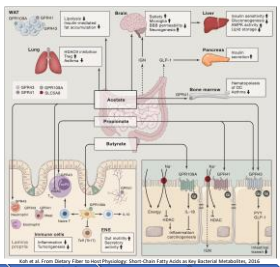
The gut microbiome and SCFAs

- 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…



1. Background | 2.Hypothesis | 3.Study design | 4. Results & Discussion | 5.Limitations | 6.Conclusion and Outlook

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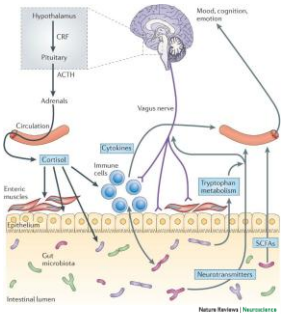
Gut-Microbiota-Brain Communication



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.

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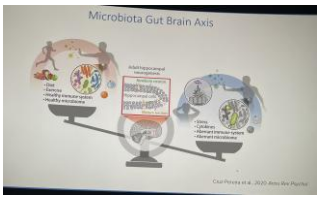
SESSION 3: Mental HEALTH

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

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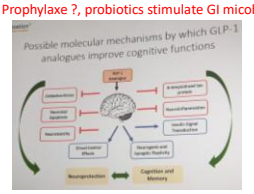
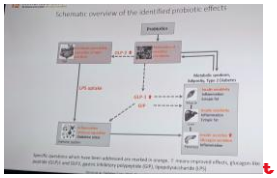
Session 8: Gut Metabolsim

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





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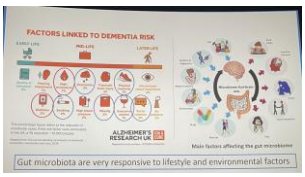
SESSION 3: Mental HEALTH

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

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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

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Interventions, examples

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

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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]

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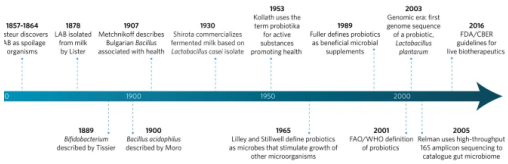

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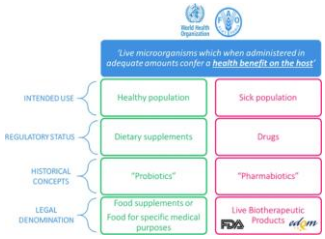
Definitions



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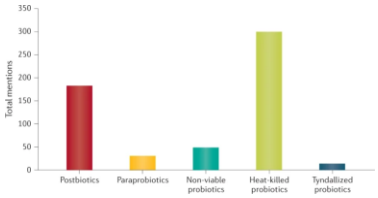

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Antimicrobial substances

- 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]

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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]

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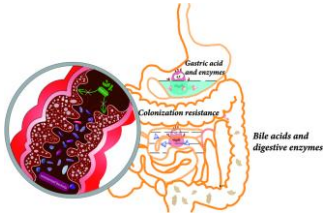

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Species

- 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]
- Escherichia 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]

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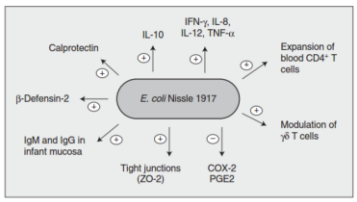

Figure 2. Various ways of immune modulation by E. coli Nissle 1917 (summary of data from in vitro and in vivo experiments) [Behnsen et al., 2013]

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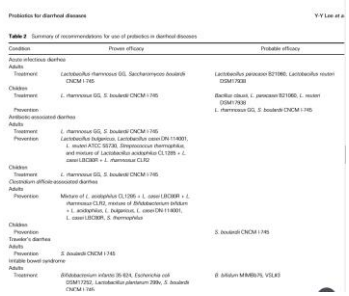

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Treatment of acute diarrhea with probiotics – meta-analyses

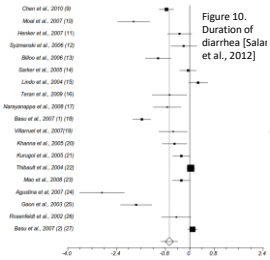

Figure 10. Duration of diarrhea [Salar et al., 2012]

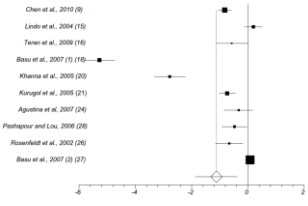

Figure 11. Duration of hospitalization [Salari et al., 2012]

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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.

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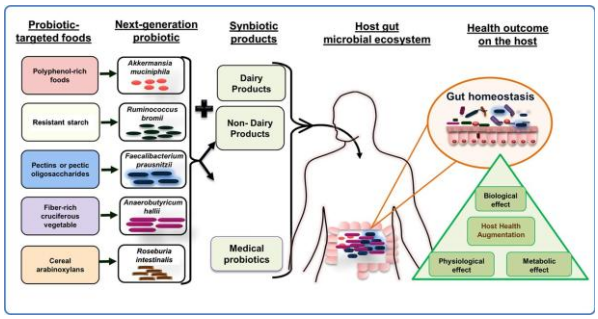

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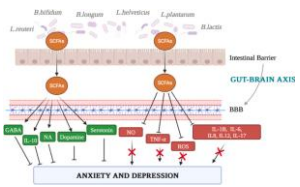
Probiotics and anxiety



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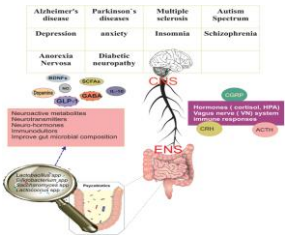

a significant decrease in depressive symptoms favoring probiotics containing strains such as Lactobacillus acidophilus, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus salivarius, Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium breve, and Bifidobacterium 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.

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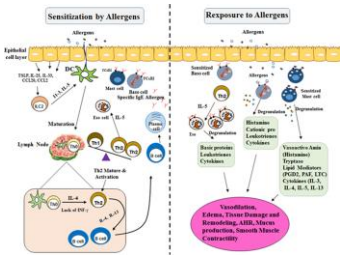

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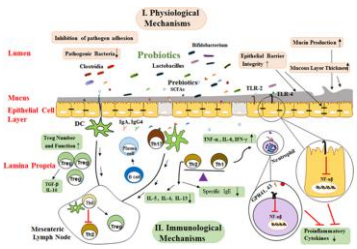

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Beneficial effects of *Lactobacillus casei* strain Shirota on academic stress-induced sleep disturbance in healthy adults: a double-blind, randomised, placebo-controlled trial

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

Received: 21 August 2016 / Accepted: 16 December 2016

OPEN ACCESS 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 Ogari-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

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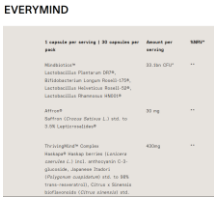

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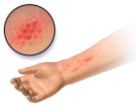
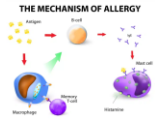
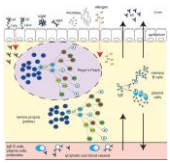
Atopic diseases, Allergy and pro-, prebiotics







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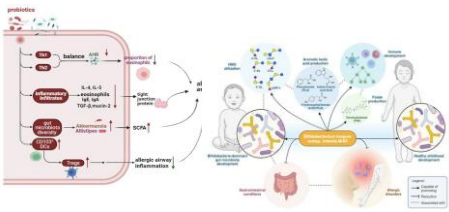
Childhood allergy, probiotics, bifibacteria



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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.

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Open Access Article

Clinical Efficacy of Probiotics for Allergic Rhinitis: Results of an Exploratory Randomized Controlled Trial

by Lisa Lungaro [1,*], Patrizia Maltz [2,3], Francesca Manza [1], Anna Costanzini [1], Guido Valentino [1], Diletta Francesca Squarzanti [2], Elisa Viciani [3], Alena Velichevskaya [3], Andrea Castagnetti [3,4], Marianna Barbalinardo [4,5], Denis Gentili [4,5], Alessio Cariani [3,5], Sara Ghisellini [3], Fabio Caputo [1], Roberto De Giorgio [1,6] and Giacomo Caio [1,7]

Background: Allergic Rhinitis (AR) is an atopic disease affecting the upper airways of predisposed subjects exposed to aeroallergens. This study evaluates the effects of a mix of specific probiotics (*L. acidophilus* PBS066, *L. rhamnosus* LRH020, *B. breve* BB077, and *B. longum* subsp. *longum* BLG240) on symptoms and fecal microbiota modulation in subjects with AR. **Methods:** Probiotic effects were evaluated at the beginning (T0), at four and eight weeks of treatment (T1 and T2, respectively), and after four weeks of follow-up from the end of treatment (T3) ($n = 19$) compared to the placebo group ($n = 22$). AR symptoms and quality of life were evaluated by the mini rhinitis quality of life questionnaire (MiniRQLQ) at each time point. Allergic immune response and fecal microbiota compositions were assessed at T0, T2, and T3. The study was registered on ClinicalTrial.gov (NCT05344352). **Results:** The probiotic group showed significant improvement in the MiniRQLQ score at T1, T2, and T3 vs. T0 ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). At T2, the probiotic group showed an increase in *Dorea*, which can be negatively associated with allergic diseases, and *Fusicatenibacter*, an intestinal bacterial genus with anti-inflammatory properties (*p*-value FDR-corrected = 0.0074 and 0.013, respectively). Conversely, at T3 the placebo group showed an increase in *Bacteroides* and *Ruminococcaceae unassigned*, (*p*-value FDR-corrected = 0.033 and 0.023, respectively) which can be associated with allergies, while the probiotic group showed a significative increase in the *Prevotella*/*Bacteroides* ratio (*p*-value FDR-corrected = 0.023). **Conclusions:** This probiotic formulation improves symptoms and quality of life in subjects with AR, promoting a shift towards anti-inflammatory and anti-allergic bacterial species in the intestinal microbiota.

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Probiotics effect the Epigenetic regulation

Article

Epigenetic aspects of new probiotic concept – a pilot study

Nina Okuka [1], Verena Schob [1], Ulrike Krammer [1], Snezana Polovina [1], Mirjana Sumarac-Dumanovic [1], Neda Milinkovic [1], Ksenija Velickovic [1], Brizita Djordjevic [1], Alexander Haslberger [#1], Nevena Dj. Ivanovic [*#1]

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

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Pro-, prebiotika und SCFAS

universität wien

MASTERARBEIT / MASTER'S THESIS

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.

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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.

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Probiotics, new ways

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

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

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.

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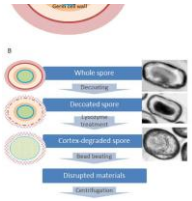
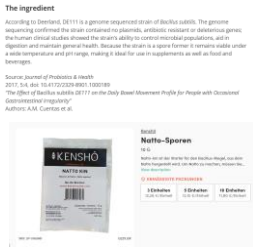
Spores





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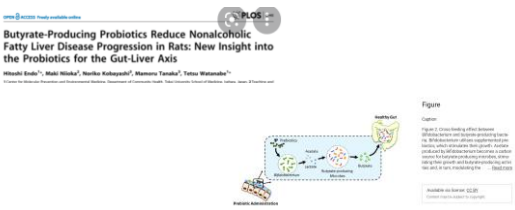
Butyrate production or cross feeding ?



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

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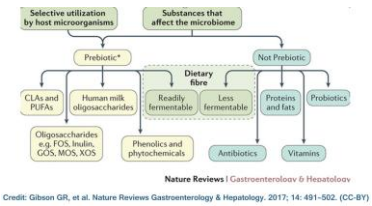
Prebiotics what is it?



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

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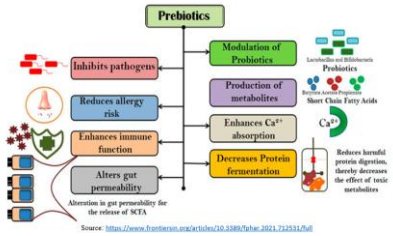

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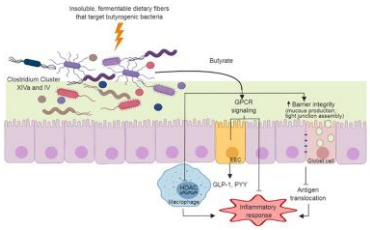
Fibers and SCFA



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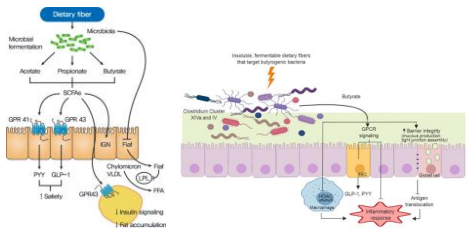
Fibers and obesity, butyrogenic



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Receptors of SCFAs

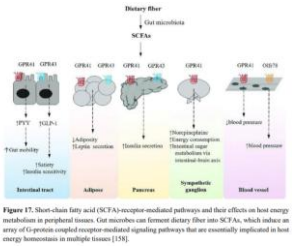

Figure 17. Short-chain fatty acid (SCFA)-receptor-mediated pathways and their effects on host energy metabolism in peripheral tissues. Gut microbes can ferment dietary fiber into SCFAs, which induce an array of G-protein coupled receptor-mediated signaling pathways that are essentially implicated in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

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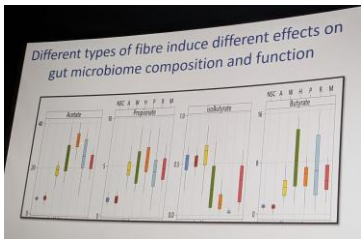

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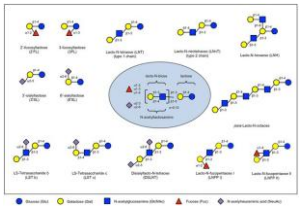
Human milk oligosaccharide composition



Human milk oligosaccharide composition blueprint. HMO composition follows a basic blueprint shown in the center. HMOs can contain 5 different monosaccharides in different number and linkages, namely glucose (blue circle), galactose (yellow circle), N-acetylactosamine (blue square), fucose (red triangle), and sialic acid (purple diamond).

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Breastmilk formula

Das Oligosaccharid, das der Muttermilch am nächsten kommt, ist derzeit das 2'-Fucosyllactose (2'-FL) – ein sogenanntes Human Milk Oligosaccharid (HMO).

Muttermilch (breast milk) ist die natürliche Nahrung für Säuglinge und enthält alle wichtigen Nährstoffe, Antikörper und Enzyme, die das Immunsystem des Babys stärken und seine Entwicklung optimal unterstützen. Sie passt sich außerdem an die Bedürfnisse des Kindes an – etwa durch Veränderungen in der Zusammensetzung während des Stillens oder über die Zeit. Formulanahrung (formula milk) ist eine industriell hergestellte Alternative, die auf Kuhmilch- oder Pflanzenbasis basiert und mit Vitaminen, Mineralstoffen und anderen Nährstoffen angereichert wird, um Muttermilch so gut wie möglich nachzuahmen. Trotz großer Fortschritte kann sie jedoch nicht alle lebenden Immunstoffe und Enzyme enthalten, die Muttermilch auszeichnen.Der Versuch, Muttermilch in der Zusammensetzung näherzukommen, konzentriert sich heute auf:Zusatz von Prä- und Probiotika, um die Darmflora zu fördern,langkettige Fettsäuren (DHA, ARA) zur Unterstützung der Gehirn- und Sehentwicklung,optimiertes Proteinverhältnis (mehr Molken- als Kaseinprotein),Zugabe von bioaktiven Komponenten wie Oligosacchariden, die das Immunsystem stärken sollen.→ Ziel dieser Entwicklungen ist es, Formulanahrung funktionell immer ähnlicher zur Muttermilch zu machen – auch wenn sie deren komplexe, lebendige Zusammensetzung noch nicht vollständig erreichen kann.

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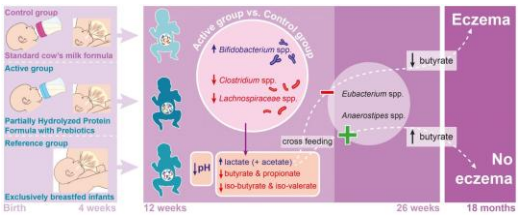
Formula: breast fed



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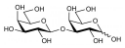
GOS



Galactooligosaccharide (GOS) sind tatsächlich ein wichtiger Bestandteil vieler Formulanahrungen, aber sie unterscheiden sich etwas von den echten Human Milk Oligosacchariden (HMOs) wie 2'-Fucosyllactose.Hier ein Überblick über GOS im Vergleich und ihre Wirksamkeit: 🏷️ Was GOS ist:GOS sind präbiotische Ballaststoffe, die meist aus Laktose (Kuhmilchzucker) industriell hergestellt werden.Sie gehören nicht zu den natürlichen HMOs der Muttermilch, wirken aber ähnlich, indem sie das Wachstum nützlicher Darmbakterien fördern – vor allem von Bifidobakterien und Lactobazillen.

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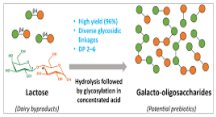

Milk replacer plus galacto-oligosaccharides significantly improved gut architectural features and villus/crypt ratio throughout the gastrointestinal tract, increased the number of goblet cells and revealed a differential abundance of beneficial probiotic bacteria, particularly Lactobacillus and Bifidobacterium.

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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.

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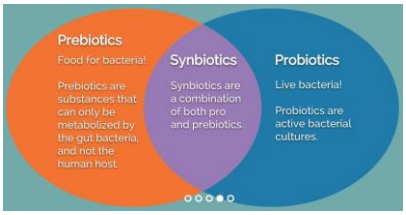
The bifidogenic effect of human milk (rich in oligosaccharides) is well-known. Prebiotics have long been added to infant milk formulas to mimic these functional characteristics of breast milk (52, 80, 81). A combination of galacto-oligosaccharide (GOS) and fructo-oligosaccharide (FOS) (scGOS 90% plus 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



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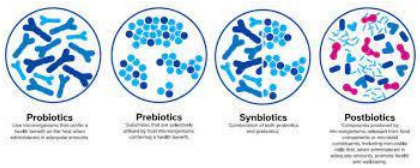

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Postbiotics

- **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)**

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Postbiotic concepts

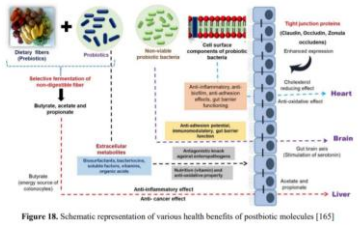

Figure 18. Schematic representation of various health benefits of postbiotic molecules [165]

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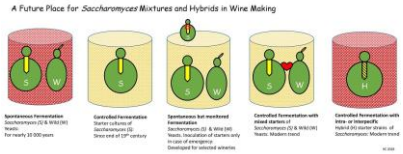
Fermentation spontaneous stater cultures



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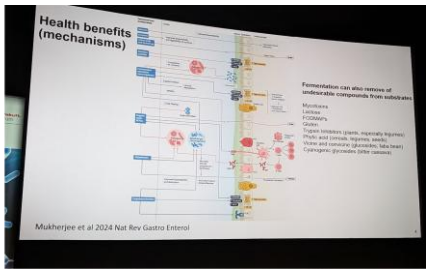

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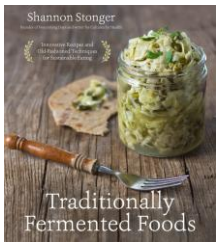
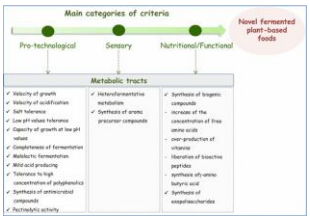
Fermentation between tradition and novel possibilities





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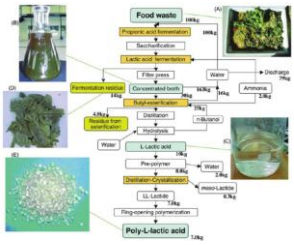
Fermentation of food waste results in usefull molecules



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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

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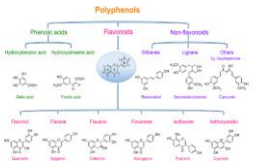
Polyphenols



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

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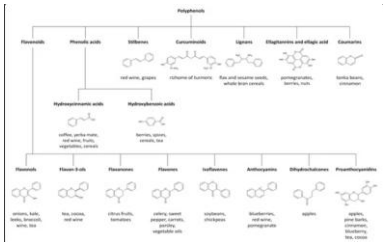
Polyphenols and their plant sources,



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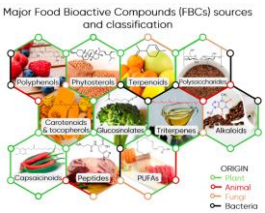
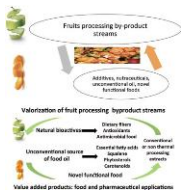
Types and classification of bioactive compounds from food





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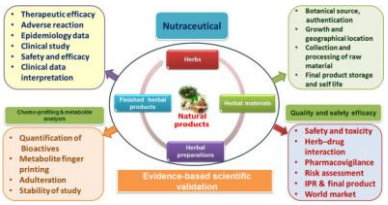
Nutraceuticals



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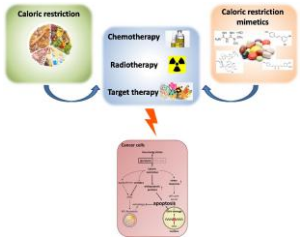
The best nutraceutical for healthy aging:CR fasting, taken as an example for desired activities



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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.

1. Background | 2.Hypothesis | 3.Study design | 4. Results & Discussion | 5.Limitations | 6.Conclusion and Outlook

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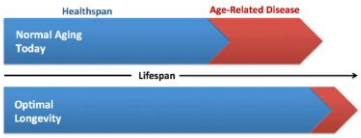
So, can we increase health span by fasting, CR ?



So what contributes to age related diseases/premature aging

1. Background | 2.Hypothesis | 3.Study design | 4. Results & Discussion | 5.Limitations | 6.Conclusion and Outlook

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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

1.Background | 2.Hypothesis | 3.Study design | 4. Results & Discussion | 5.Limitations | 6.Conclusion and Outlook

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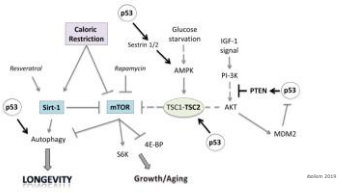
Short term Caloric restriction mechanisms : AMPK, SIRT, mTOR, p53



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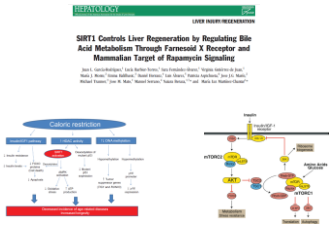
Fasting pathways: Sirt, mTOR pathways



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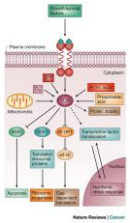
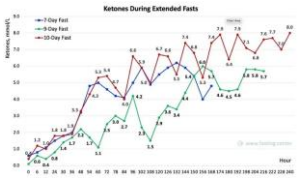
mTOR, Rapamycin immune-suppressiv, longevity relevant

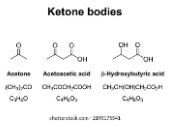


Inhibition of the protein kinase mechanistic target of rapamycin (mTOR) with the Food and Drug Administration (FDA)-approved therapeutic rapamycin promotes health and longevity in diverse model organisms.

179

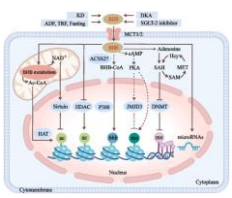
Fasting > 3 days , Buchinger fasting, production of Butyrate and ketogenic molecules

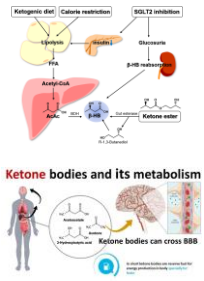




180

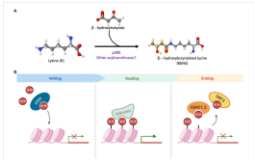
Ketone bodies





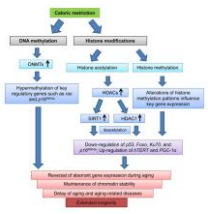
181

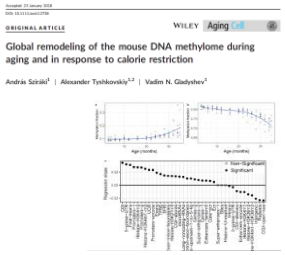
Histones, Aging



182

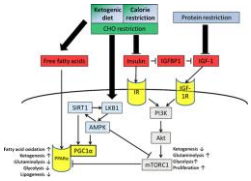
Caloric restriction, fasting and aging change epigenetic CpG -methylation structure

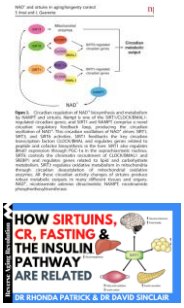




183

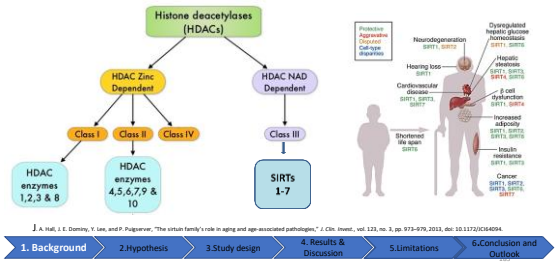
Fasting and sirtuins





184

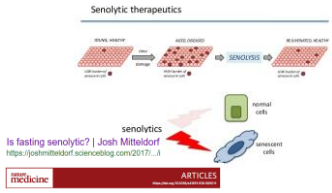
Histone deacetylases, Sirtuins



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.

185

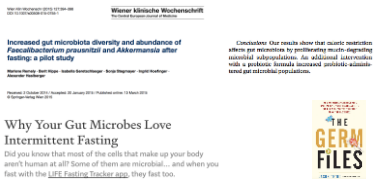
Caloric restriction: Rejuvenetion by senolysis? role for autophagy ?



83rd ICREA Colloquium, 2018

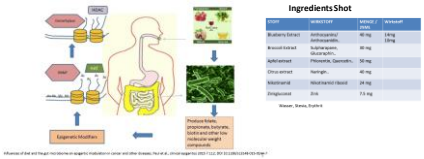
186

Fasting and Microbiota



187

Effect of Plant Ingredient and Diet on Microbiota and Metabolites



188

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


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

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

Wasser, Stevia, Erythrit

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

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

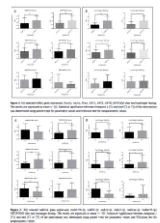
Active (N. 131) Placebo (n: 30)
Intervention 3 months

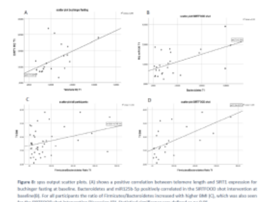
Feces, Blood spots before, after 1,3 month

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

189

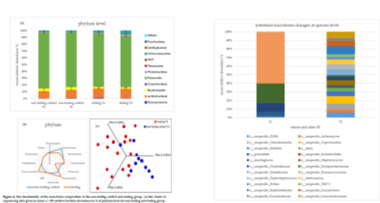
positive correlation of the abundance of butyrate-producing *Bacteroidetes* with Mir125, siRT-1 expression, telomere length





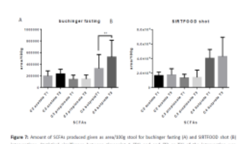
190

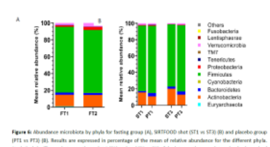
Buchinger fasting resulted in a rise in the distribution of Proteobacteria, increased microbiota diversity and a significant increase in Christensenella



191

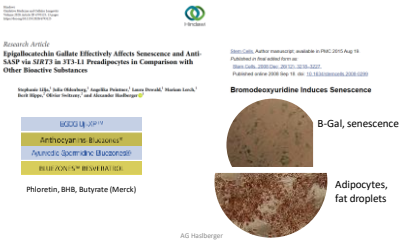
3M sirt inducing drink increased *Actinobacteria.*
Firmicutes/*Bacteroidetes* ratio decreased and correlated with BMI. Only Fasting increased Butyrate significantly





192

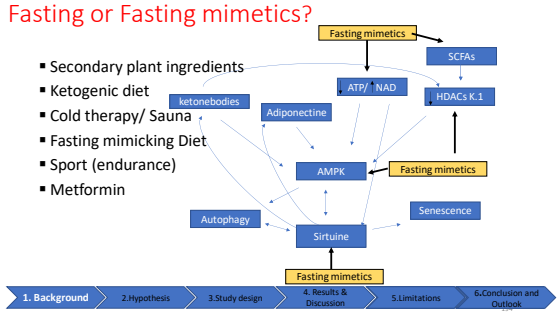
STUDY SENOLYTICS, SENESCENCE MARKERS IN BRDU TREATED PRE-ADIPOCYTES, ADIPOCYTES, 3T3



193

Fasting or Fasting mimetics?

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



194

CR, fasting mimetics

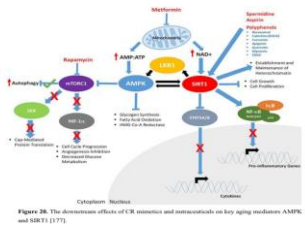


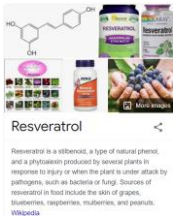
Figure 20. The downstream effects of CR mimetics and nutraceuticals on key aging mediators AMPK and SIRT1 [177].

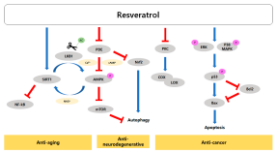
195

Aging, longevity , big business, science

196

Examples,
Resveratrol

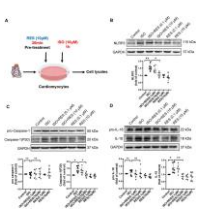


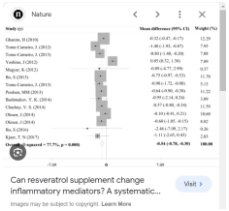


Previous studies have demonstrated that resveratrol is well-absorbed following oral administration, with ~75% of the dose absorbed. Following absorption, resveratrol undergoes rapid and extensive metabolism leading to low bioavailability

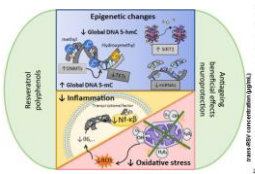
197

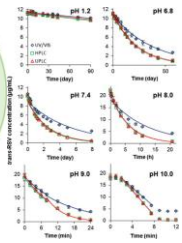
Resveratrol Vitro : Vivo

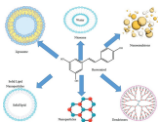




198



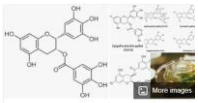


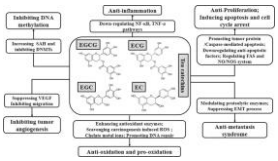


Novel food ?!

199

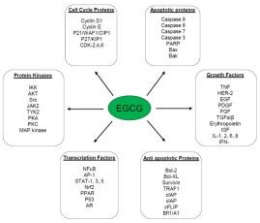
Green tea extract, EGCG, Catechines





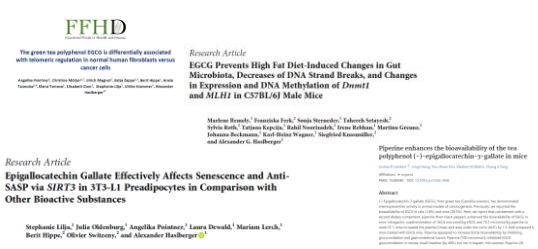
200

EGCG



201

EGCG II


FFHD

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

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

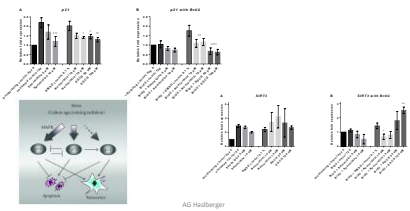
Research Article

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

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

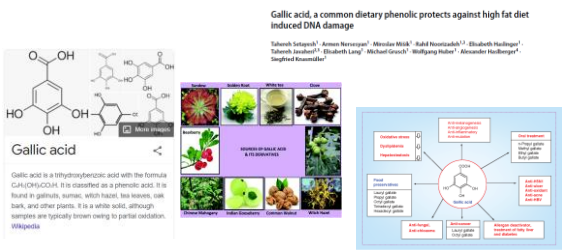
202

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



203

Gallic acid



204

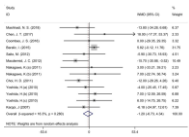
Astaxanthin

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

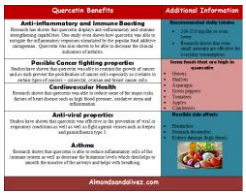
Das Carotinoid ist jedoch nicht nur im Plankton enthalten, sondern gelangt über die Nahrungskette in das Tierreich. Wassertiere wie Lachs, Garnelen, Forellen, Krill oder Krebse, aber auch Flamingos fressen die Mikroalge. Sie erhalten durch Astaxanthin ihre rötliche Färbung und schützen sich damit ebenfalls 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

205



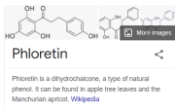
206

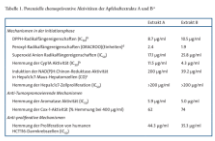
Quercetin



207

Phloretin





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

208

Food & Function

ROYAL SOCIETY OF CHEMISTRY

PAPER

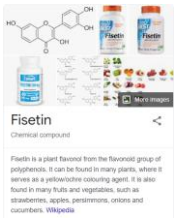
Assessment of human inter-individual variability of phloretin metabolites in urine after apple consumption. AppleCOR study†

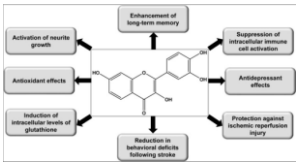
: This study aimed to assess the inter-individual variation in phloretin absorption and metabolism and to seek possible phloretin metabotypes following apple snack consumption. Methods: The excreted phloretin metabolites in 24 h urine samples were determined by UPLC-MS/MS in 62 volunteers after acute 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.

209

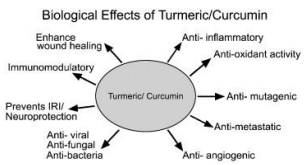
Fisetin





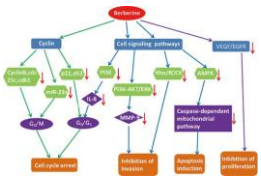
210

Curcumin



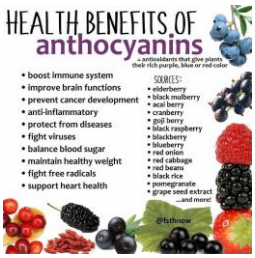
211

Berberin, Berberitze



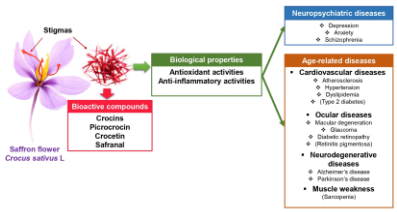
212

Anthocyans



213

Saffron



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Spermidin

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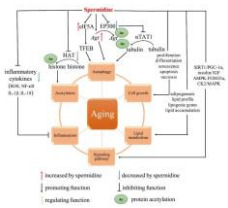
Spermidin mechanisms



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, insuli n/ IGF, AMPK-FOXO3a, and CK2/MAPK signaling pathways.

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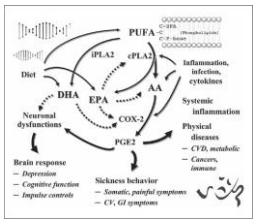
Fishoil, EPA, DHA



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Longevity and beyond

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Bluezones

Blaue Zonen sind Regionen der Welt in denen Menschen viel länger als der Durchschnitt leben sollen. Das Konzept wird von Dan Buettner vertreten und wurde erstmals im November 2005 im Magazin National Geographic in der Titelgeschichte „The Secrets of a Long Life" von Buettner vorgestellt.

Buettner identifizierte fünf Regionen, die er als „Blaue Zonen" betrachtet: Okinawa (Japan), Sardinien (Italien), die Nicoya-Halbinsel (Costa Rica), Ikaria (Griechenland) und unter den Siebenten-Tags-Adventisten in Loma Linda, Kalifornien.

Er gibt eine Erklärung, basierend auf Daten und Beobachtungen aus erster Hand, warum diese Bevölkerungs-gruppen gesünder und länger leben.

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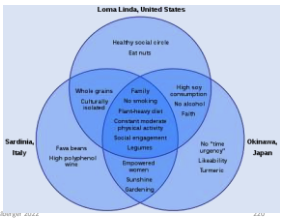
Von den Bluezones lernen wir persönliche, regional spezifische Massnahmen gegen vorzeitiges Altern, alters-bedingte Erkrankungen, Zentral: bioaktive Moleküle



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Die Menschen in den Blauen Zonen haben gemeinsame Lebensstil-Merkmale, die zu ihrer Langlebigkeit beitragen. Sechs gemeinsamen Merkmale der Menschen in Okinawa, Sardinien und den Blauen Zonen von Loma Linda:

- Familie – wichtiger als andere Anliegen
- Nicht rauchen
- Pflanzenbasierte Ernährung – der Großteil der verzehrten Nahrung stammt aus Pflanzen.
- Ständige moderate körperliche Aktivität – ein untrennbarer Bestandteil des Lebens.
- Soziales Engagement – Menschen jeden Alters sind sozial aktiv und in ihre Gemeinschaften integriert.
- Hülsenfrüchte – häufig konsumiert

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Buettner: Faktoren die den Lebensstil der Menschen in den blauen Zonen behandeln:

- Mäßige, regelmäßige körperliche Aktivität.
- Lebensinhalt.
- Stressabbau.
- Mäßige Kalorienzufuhr.
- Pflanzenbasierte Ernährung.
- Mäßiger Alkoholkonsum; überwiegend Wein.
- Engagement in der Spiritualität oder Religion.
- Engagement im Familienleben.
- Engagement im gesellschaftlichen Leben.

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Bluezones limitations

Das Bluezones Konzept wurde durch Arbeiten von Gianni Pes und Paulain 2004 im Journal of experimental Gerontology erstmals erstellt. Dan Buettner, Gründer von BlueZones.com und mehrfacher New York Times Bestseller-Autor baute auf deren demografische Arbeit auf. Kritik kam unter anderem von Harriet Hall 2021. Sie schrieb für Science-Based Medicine, dass es keine kontrollierten Studien über die Hundertjährigen in den Blue Zones gäbe und dass die Ernährung in den Blue Zones auf Spekulationen und nicht auf Beweisen durch eine strenge wissenschaftliche Methode beruhe.
Ich teile deshalb die Bedenken von SJ Newman und bin sehr froh, dass auch seine Kritik zu einer genaueren Evaluation der Daten auf denen das Bluezones Konzept beruht führen wird.
Leider ist es richtig, dass Daten, die so lange in die Vergangenheit reichen wie zB das Alter schwierig sind und z.B. viele Daten während des Weltkrieges verloren gingen. Besonders sind auch die Ernährungsgewohnheiten von sehr vielen Faktoren abhängig. Lifestyle und Ernährung können kaum voneinander getrennt werden. Neue bioinformatische Analysemethoden werden hier verbesserte Aussagen bringen und vielleicht auch neue Regionen einbeziehen. Auch fehlen die Konsequenzen von persönlichen Einflüssen (siehe mein Buch personalised nutrition). Und die neuen Möglichkeiten und Analysemethoden der Epigenetik müssen in ein überarbeitetes Bluezones Konzept eingebracht werden.

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D. Sincliar and the endless life

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Scientific Innovations & Theories of David Sinclair

1.Sirtuins and NAD⁺ Pathway

1. Sinclair has done foundational work on **sirtuins**, a class of proteins (enzymes) that are NAD⁺-dependent deacetylases. sinclair.hms.harvard.edu+2nad.com+2
2. His lab showed that as organisms age, **NAD⁺ levels decline**, which impairs sirtuin function. PubMed+1
3. By boosting NAD⁺ (e.g., via NAD⁺ precursors like **NMN**), sirtuins can be reactivated, which in turn supports genomic stability, stress resistance, metabolic health, and potentially longevity. providence.elsevierpure.com+2nad.com+2
4. He also helped discover **sirtuin-activating compounds (STACs)**, such as resveratrol and synthetic molecules (e.g., SRT1720), which can enhance the activity of SIRT1. nad.com+1

2.Information Theory of Aging / Epigenetic Reprogramming

1. Sinclair has contributed to a provocative theory often called the **"Information Theory of Aging."** The idea: aging is not just about accumulating damage (mutations) but about the **loss of epigenetic information** — i.e., the "software" of our cells becomes corrupted. PMC+2PubMed+2
2. In a landmark 2023 Cell paper, his team showed that artificially inducing DNA double-strand breaks in mice (without causing mutations) can make their cells "age" (in terms of their epigenetic landscape), but that this process can be **reversed** by reprogramming factors (partial Yamanaka factors). PMC
3. This suggests that some aspects of aging are **reversible**, because the "backup" epigenetic instructions are still there and can be "rebooted." TIME+1
4. This idea is also being translated into experiments: for instance, Sinclair's lab has done **partial cellular reprogramming** (using 3 of the 4 Yamanaka factors) in mice to restore more youthful epigenetic patterns without turning cells fully into stem cells. TIME

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Key Recent Molecules / "Recipes" in Sinclair's Age-Reversal Thinking

1.Chemical Cocktails for Epigenetic Reprogramming

1. In a 2023 paper, Sinclair's lab (Yang et al.) reported **six chemical cocktails** that, in human/senescent cells, restored a more youthful gene expression profile *within a week*. Aging-US+2PMC+2
2. Importantly, these cocktails didn't erase cell identity (i.e., they didn't fully turn cells into stem cells) — they partially reprogrammed them. Aging-US
3. The base (or "core") small molecules used in these cocktails include:
   1. **Valproic acid (VPA)** — a histone deacetylase (HDAC) inhibitor. PMC+1
   2. **CHIR-99021** — a GSK3α/β inhibitor, which affects signaling pathways. PMC+1
   3. **E-616452** (also called *RepSox*) — a TGF-β signaling pathway inhibitor. PMC
   4. **Tranylcypromine** — affects histone modification / epigenetics. PMC
   5. **Forskolin** — increases cAMP (activates adenylyl cyclase). PMC
4. In addition to these, different cocktails also included: **TTNPB**, **Y-27632**, **SAG (Smoothened agonist)**, **ABT-869**, **sodium butyrate**, **α-ketoglutarate**. ResearchHub
5. Concentrations used in their cell experiments (in vitro) included, for example: VPA ~ 250 μM, CHIR99021 ~ 10 μM, RepSox ~10 μM, Tranylcypromine ~ 5 μM, Forskolin ~ 50 μM. ResearchHub

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1.Optimized / Minimal Cocktail (2-Compound)

1. More recently (discussed by community sources and follow-up analysis), there is mention of a **"2-compound" (2c) cocktail** that is a simplified version of the 7-molecule mix. According to a summary: **RepSox + Tranylcypromine** alone may be sufficient to restore several aging phenotypes (genomic instability, epigenetic dysregulation, senescence, oxidative stress) in cells. Fight Aging!
2. This is significant because a smaller, simpler cocktail may be easier to develop more safely, but *this is still very early-stage research*. Fight Aging!+1

2.Other "Stack" Molecules Outside Reprogramming

Besides the reprogramming cocktails, Sinclair often talks about more classical longevity molecules / supplements:

1. **NAD⁺ precursors**: NMN (nicotinamide mononucleotide) and NR (nicotinamide riboside) remain central. nad.com+1
2. **Spermidine**: which stimulates autophagy. nad.com
3. **Metformin**: Sinclair includes this in his "stack." nmn.com+1
4. **Senolytics / other drugs**: In a summary of "8 anti-aging medicines," his group (with other researchers) names rapamycin, GLP-1 agonists (e.g. Ozempic), senolytic-like molecules. nad.com

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1. Stem Cell Exhaustion & Rejuvenation

Aging is closely linked to the *decline in both number and function* of stem cells (hematopoietic, muscle satellite cells, neural stem cells, mesenchymal stem cells).

Approaches:

•**Reactivating dormant stem cells**

Using signals like Wnt, Notch, or TGF-β inhibitors to restore youthful function.

•**Reducing stem cell senescence**

Removing senescent cells (with senolytics) can restore a more youthful stem-cell niche.

•**Niche rejuvenation**

Repairing the microenvironment that stem cells depend on—ECM, signaling molecules, inflammation levels.

2. Stem Cell Replacement or Transplantation

Replacing aging stem cell pools with younger or engineered cells.

Examples:

•**Hematopoietic stem cell (HSC) transplantation**

Can partially rejuvenate immune function.

•**Mesenchymal stem cell (MSC) therapies**

Reduce inflammation, modulate immune response, and support tissue repair.

•**Induced pluripotent stem cells (iPSCs)**

Reprogrammed from adult cells; can be converted into youthful, patient-specific tissue.

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3. Partial Cellular Reprogramming ("Yamanaka Reset")

A groundbreaking concept:
Short pulses of Yamanaka factors (OSKM) can *rejuvenate cells without wiping identity*.
Effects observed in research:
•Reduced epigenetic age
•Improved mitochondrial function
•Enhanced tissue repair
•Reversed age-associated gene expression
The challenge:
Avoiding tumor formation by **preventing full reprogramming**.

4. Tissue Engineering & Organoid Replacement
Instead of repairing in place, you *grow replacement tissue* using stem cells.
Examples:
•Organoids for liver, kidney, or gut
•Engineered skin or cartilage
•Lab-grown thymus for immune rejuvenation
This allows **young, functional tissue** to replace aged structures.

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5. Clearing Damaged Cells to Support Stem Cell Health
Stem cells decline partly due to:
•Inflammation
•Accumulated DNA damage
•Senescent cell burden
•Mitochondrial dysfunction
Approaches:
•**Senolytics** (remove senescent cells)
•**Autophagy boosters** (rapamycin, fasting mimetics)
•**Redox balance / mitochondrial repair**
These create a cleaner "internal environment" that supports stem cell renewal.

6. Gene Editing to Enhance Stem Cell Longevity
Using CRISPR or epigenetic editing to modify stem cell behavior.
Concepts:
•**Boost genomic stability**
•**Increase telomerase expression**
(Carefully—raises cancer risk if uncontrolled)
•**Correct age-associated mutations**
•**Enhance DNA repair pathways (e.g., SIRT6, FOXO3)**

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7. Secretome & Exosome-Based Rejuvenation

Stem cells release **exosomes** containing growth factors, microRNAs, and signaling molecules.

Potential effects:
•Reduced inflammation
•Enhanced tissue repair
•Improved collagen production and wound healing
•Mitochondrial transfer to damaged cells
This allows *rejuvenation without transplanting live cells*.

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The Yamanaka factors are a set of four genes (\(Oct4,Sox2,Klf4,\) and \(c-Myc\)) that can reprogram adult cells into induced pluripotent stem cells (iPSCs).

Discovered by Nobel laureate Shinya Yamanaka, these factors allow mature, specialized cells to be reverted to a stem cell-like state, where they can differentiate into any cell type in the body.
This discovery has applications in regenerative medicine, cellular aging, and disease modeling.
The four factors: The specific transcription factors are Oct4, Sox2, Klf4, and c-Myc.

The process: They work by altering the cell's chromatin structure to erase its previous specialized identity and activate the genes required for pluripotency. This process, known as cellular reprogramming, allows a differentiated cell to become a pluripotent stem cell. Significance: This discovery won Shinya Yamanaka the 2012 Nobel Prize in Physiology or Medicine and has opened up new avenues in research.

Applications: Yamanaka factors are being explored for applications such as: Generating patient-specific stem cells for research and therapies. Developing disease models. Regenerating tissue, such as in the central nervous system or heart, by promoting cell regeneration. Challenges: While promising, there are challenges, including potential tumor formation from c-Myc and optimizing the efficiency and safety of the reprogramming process.

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von ATP in den Mitochondrien, den Kraftwerken der Zelle.Es fungiert als Kofaktor in der Glykolyse, dem Citratzyklus und der Atmungskette.In diesen Prozessen nimmt NAD\({}^{+}\) Elektronen und Protonen auf, wird dabei zu NADH reduziert, und transportiert die Energie dann zur Atmungskette, wo ATP produziert wird. 2. DNA-Reparatur NAD\({}^{+}\) spielt eine zentrale Rolle bei der Reparatur geschädigter DNA-Strukturen.Es reguliert die Wechselwirkung zwischen den Proteinen PARP1 und DBC1, wodurch die Aktivität von PARP1 für die Reparatur ermöglicht wird. 3. Zellschutz und Antioxidative Wirkung Die reduzierte Form NADH wirkt als starkes Antioxidans und schützt die Zellen vor schädlichen freien Radikalen und oxidativem Stress.Dies kann dazu beitragen, die Zellalterung zu verlangsamen. 4. Unterstützung des Nervensystems Das Nervensystem ist auf NAD\({}^{+}\) angewiesen, um die Signalübertragung zu unterstützen.Es hilft, Nervenzellen vor oxidativem Stress zu schützen, was mit besserer Konzentrationsfähigkeit und mentaler Klarheit verbunden ist. 5. Stoffwechsel und Anti-Aging NAD\({}^{+}\) ist an der Umwandlung von Nahrung in Energie beteiligt.Da die NAD-Spiegel mit dem Alter abnehmen, wird die Aufrechterhaltung eines ausreichenden Spiegels als Weg angesehen, um Alterungsprozesse zu verlangsamen. Formen von NAD NAD+ (oxidierte Form): Nimmt Elektronen und Protonen von anderen Molekülen auf.
NADH (reduzierte Form): Entsteht durch die Aufnahme von Elektronen und Protonen durch NAD+.NAD-Vorstufen: Substanzen wie Nicotinamid-Ribosid (NR) und Nicotinamid-Mononukleotid (NMN) können vom Körper in NAD\({}^{+}\) umgewandelt werden, um dessen Spiegel zu erhöhen.

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8. Restoring Regeneration Seen in Youth

Many animals (salamanders, zebrafish) regenerate limbs or organs through:
•Local stem cell activation
•Controlled dedifferentiation
•Growth factor cascades
Scientists aim to "unlock" similar regenerative programs in adult humans.

Molecular basis of positional memory in limb regeneration

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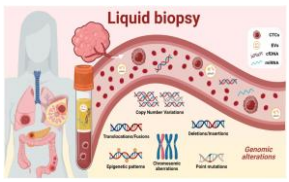
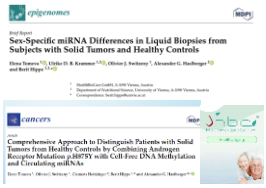
Epigenetics in early cancer diagnosis: Combination of markers from different OMICS improves prediction: SNPS, CPG methylation, miRNAs from liquid biopsies





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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	

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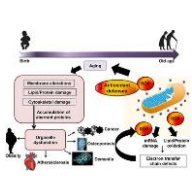
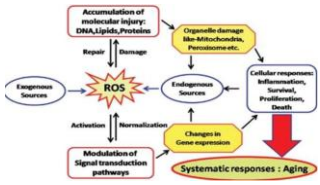
ROS and antioxydative activities





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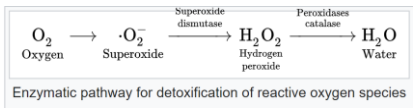
Antioxydants

Antioxidant	Solubility	Concentration in human serum (μM)	Concentration in liver tissue (μmol/kg)
Ascorbic acid (vitamin C)	Water	50–60[111]	260 (human)[54]
Glutathione	Water	4[111]	6,400 (human)[54]
Lipoic acid	Water	0.1–0.7[112]	4–8 (rat)[57]
Uric acid	Water	200–400[113]	1,600 (human)[54]
Carotenes	Lipid	β-carotene: 0.5–1[114] retinol (vitamin A): 1–3[115]	5 (human, total carotenoids)[51]
α-Tocopherol (vitamin E)	Lipid	10–40[60]	50 (human)[54]
Ubiquinol (coenzyme Q)	Lipid	5[112]	200 (human)[55]



Enzymatic pathway for detoxification of reactive oxygen species

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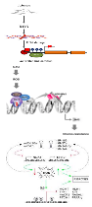
Ros, stress impairs all mechanisms of the epigenetic machinery - > **aging**



Promotor CpG methylation

Histones

DNA - packaging

Non-coding miRNAs

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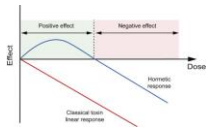
Stress and Mitormesis



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.

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Antioxydants, mithormesis


Antioxidants

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.

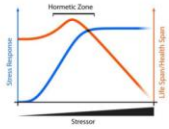

Figure 11. Mithormesis Theoretical curve showing how low doses of a stressor may have beneficial effects by activating intracellular stress response pathways. If the stressor exceeds the capacity of the stress response system to maintain homeostasis, then deleterious phenotypes are observed.

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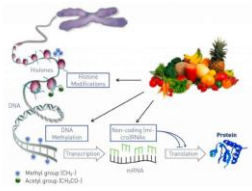
Novel foods, functional foods and epigenetics



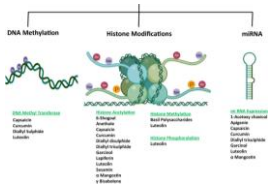


Figure 4. Polyphenols address all epigenetic mechanisms.

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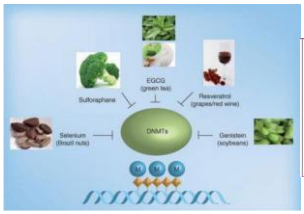
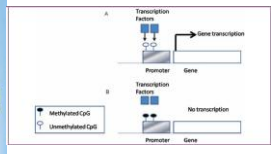
DNA, CpG methylation





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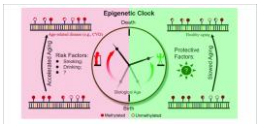
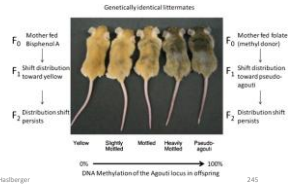
Best marker for aging: The epigenetic clock (Horvath) evaluates the biological age, accelerated or decelerated, healthy aging (CpG methylation of 100s of genes)





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Effects on histones, chromation

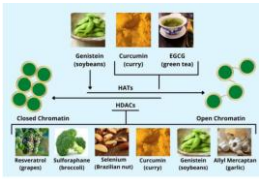

Figure 6. Effects of epigenetic active plant ingredients on histones, chromatin, and gene expression

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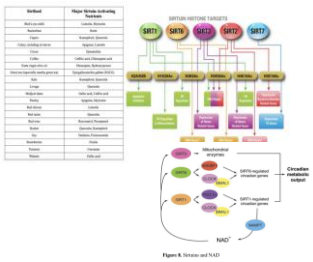
Sirtuins



Figures 8. Sirtuins and NAD

BCHD

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

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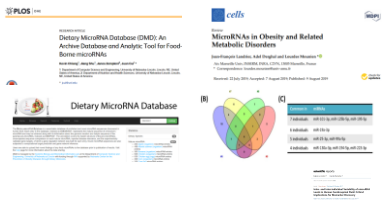
Epigenetic miRNAs: food borne, marker for mechanisms, phenotypes, disorders



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Mi RNAS, non coding RNAs

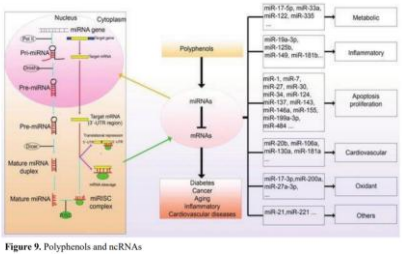
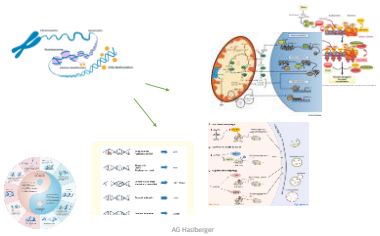


Figure 9. Polyphenols and ncRNAs

249

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



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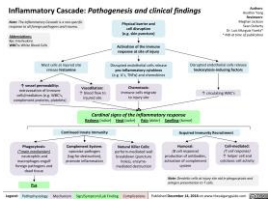
Polyphenols and Inflammation mechanisms



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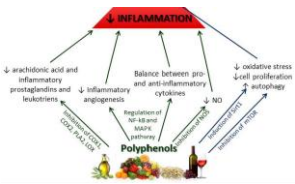
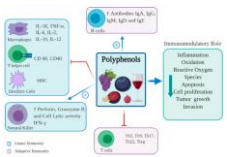
Polyphenol effects inflammation:





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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.

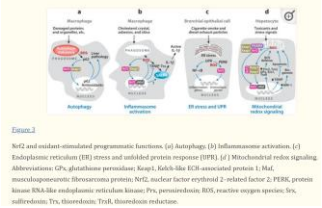

Figure 2

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.

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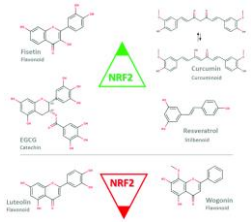
NRF2 agonists, antiagonists



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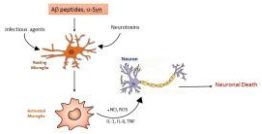
Neuro- inflammation



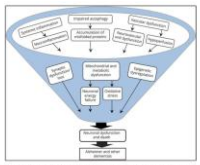


Figure 1. Microglial cells respond differently depending upon type and intensity of activation signals. [87].

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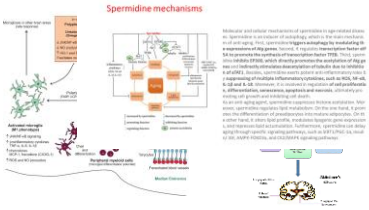
Polyphenols, spermidin and microglia



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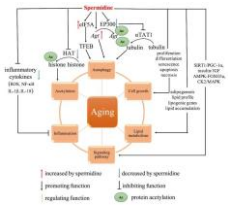
Spermidine mechanisms



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 eIF5A to promote the synthesis of transcription factor TFEB.** Third, spermidine **inhibits EP300, which directly promotes the acetylation of Atg genes** and **in directly stimulates deacetylation of tubulin due to inhibition of αTAT1.** 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.

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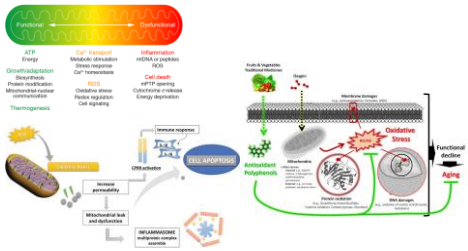
Polyphenols and mitochondria, the oldest theory of aging



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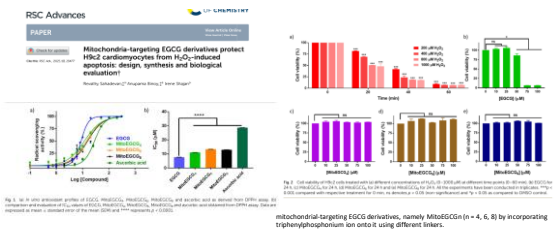
Mitochondria directed EGCG protects from H2O2 induced cell apoptosis



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

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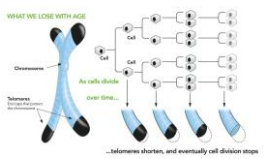
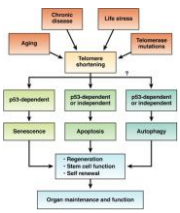
Telomer attrition





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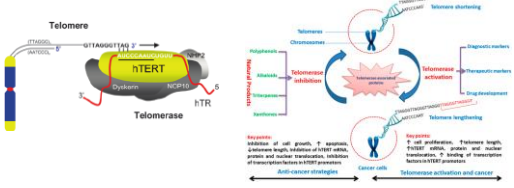
Telomers, telomerase



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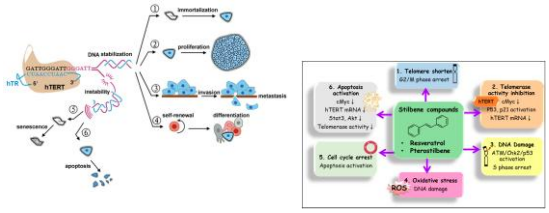
Polyphenols in the regulation of telomerase, hTERT



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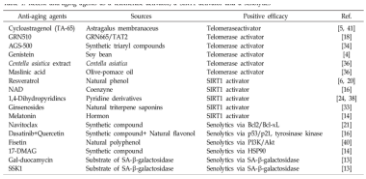

Anti-aging agents	Sources	Positive efficacy	Ref.
Cycloastragenol (TA-65)	Astragalus membranaceus	Telomeraseactivator	[5, 41]
GRN510	GRN665/TAT2	Telomerase activator	[38]
AG56-500	Synthetic triaryl compounds	Telomerase activator	[34]
Genistein	Soy bean	Telomerase activator	[4]
Centella asiatica extract	Centella asiatica	Telomerase activator	[36]
Maslinic acid	Olive-pomace oil	Telomerase activator	[36]
Resveratrol	Natural phenol	SIRT1 activator	[6, 20]
NAD	Coenzyme	SIRT1 activator	[16]
1,4-Dihydropyridines	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	[34]
Gal-dasocamycin	Substrate of SA-β-galactosidase	Senolytics via SA-β-galactosidase	[13]
SSK1	Substrate of SA-β-galactosidase	Senolytics via SA-β-galactosidase	[13]

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EGCG telomerase, cmyc, hTERT

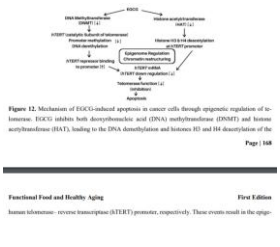

Figure 12. Mechanism of EGCG-induced apoptosis in cancer cells through epigenetic regulation of telomerase. EGCG inhibits both deoxyribonucleic acid (DNA) methyltransferase (DNMT) and histone acetyltransferase (HAT), leading to the DNA demethylation and histones H3 and H4 deacetylation of the

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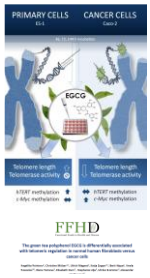
human telomerase - reverse transcriptase (hTERT) promoter, respectively. These events result in the epige-



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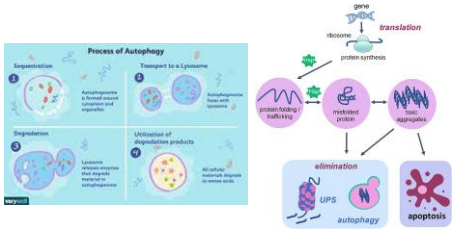
Autophagy, apoptosis



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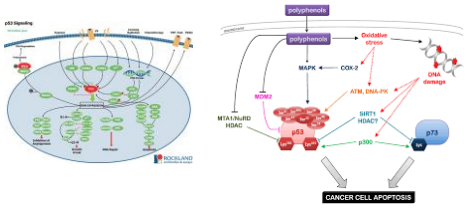
Apoptosis, p53 and polyphenols



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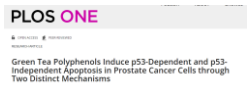

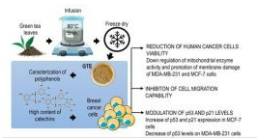

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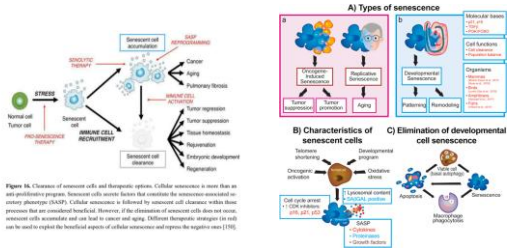
Senescence and polyphenols



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Polyphenols and senescence

Review

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

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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.

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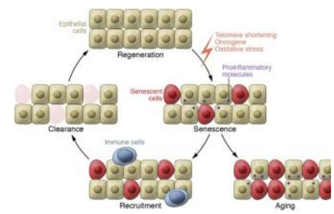
Senolytics between rejuvention of tissues and cancer prevention

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

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
	Paucifloral 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/AKT1/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	5 (μg/mL)	ATF4/DDIT3/TRIB3/AkT/mTOR



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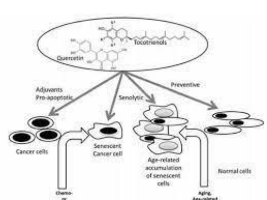
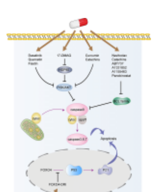
Quecetin, senolytics and markets millio $ markets





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Immuno senescence and nutraceuticals

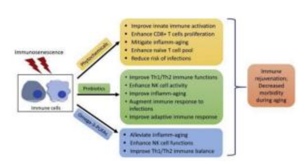

Figure 13. Nutraceuticals-Based Immunotherapeutic Concepts and Opportunities for the Mitigation of Cellular Senescence and Aging

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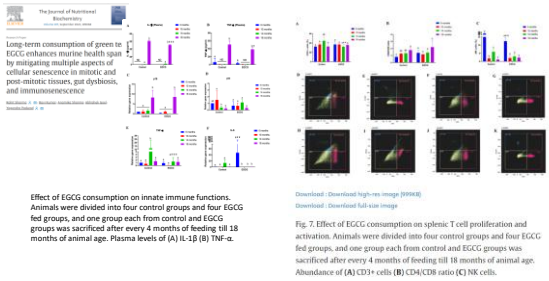

Effect of EGCG consumption on innate immune functions. Animals were divided into four control groups and four EGCG fed groups, and one group each from control and EGCG groups was sacrificed after every 4 months of feeding till 18 months of animal age. Plasma levels of (A) IL-1β (B) TNF-α.

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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.

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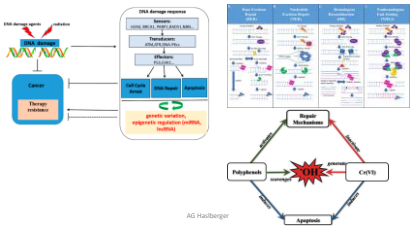
Aging DNA-damage response, DNA-repair, Epigenetics, Polyphenols



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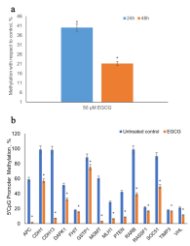
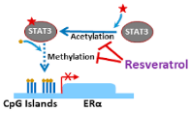
MGMT and MLH1 DNA repair enymes and promotor methylation, EGCG





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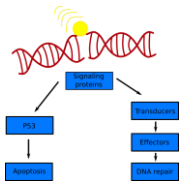
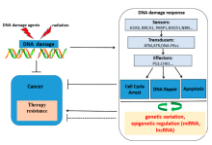
Epigenetics regulates DNA repair





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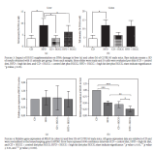
Mouse study: EGCG reduced high fat diet induced strandbreaks, DNmt1, comet assay

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



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Aging, ageotypes and prevention

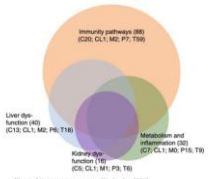

Figure 21. Ageotypes, personalized aging [186]

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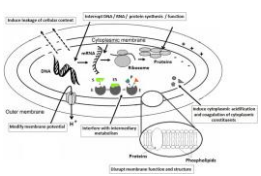
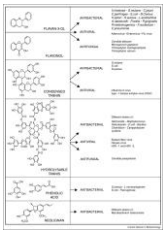
Anti bacterial polyphenols





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Antiviral nutraceuticals

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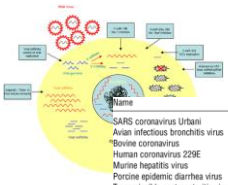
RNA and Corona viruses



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)

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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[17]
2	Quercetin	SARS-CoV S2 protein	HIV-luc/SARS pseudotype virus assay	EC_{50} of 89.4 μM and CC_{50} of 3.32 mM	Yi et al, 2004[17]
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[18]
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[18]
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[18]
6	Resveratrol	MERS-CoV hP	• MTT assay using vero-B4 cell line • Nucleocapsid protein staining	• Found to be effective in the 135–150 μM range on viral titre as well as viral RNA amount. • Inhibits caspase 3 cleavage.	Lin et al, 2017[19]
7	Hesperetin	SARS-CoV 3CLPro	Cell free and cell-based cleavage assays	IC_{50} of 40 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[20]
8	Quercetin	ACE2 and PARN	• Gene silencing • Expression studies • Transgenic mouse models	• Quercetin affected ACE2 expression. • In addition, it was found to alter the expression of 98 of 331 (30%) genes encoding human proteins that serve as target for the SARS-CoV-2.	Ghosh, 2020[21]

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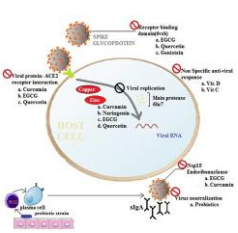
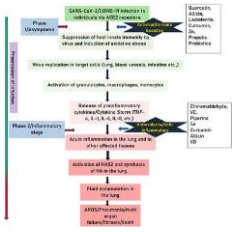
Covid , SARS-2





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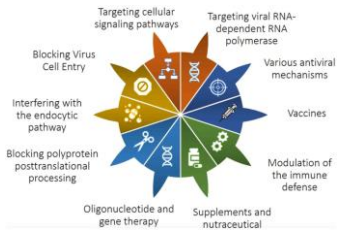
Strategies



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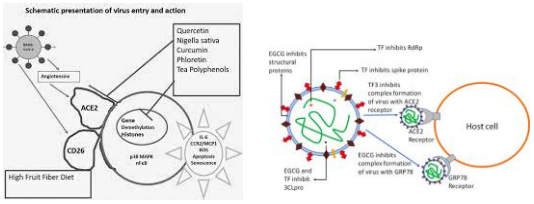
Nutraceuticals, epigenetics and inhibition of RNA viruses



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

A.G. Haslberger 2021

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.

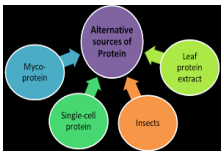
Epub 2016 Nov 2.

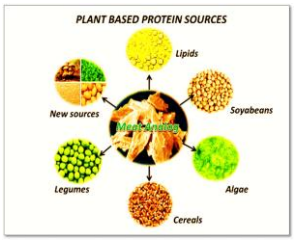
Physiological effects of epigallocatechin-3-gallate (EGCG) on energy expenditure for prospective fat oxidation in humans: A systematic review and meta-analysis

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





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A mega market

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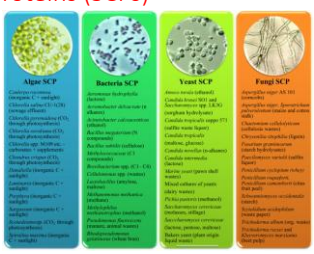
Proteins from microorganisms , single-cell proteins (SCPs)



Plant- and fungus-based substitutes are frequently made with soy (e.g. tofu, tempeh, and textured vegetable protein), but may also be made from wheat gluten as in seitan, pea protein as in the Beyond Burger, or mycoprotein as in Quorn.

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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

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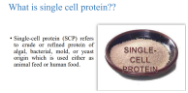
Single cell proteins



- 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.

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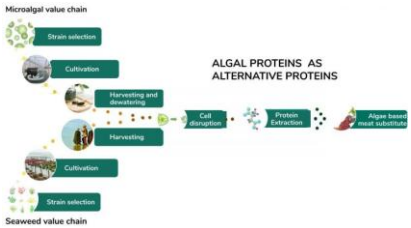
Protein (and other goodies) from algae



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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

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Microalgae as a novel food

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

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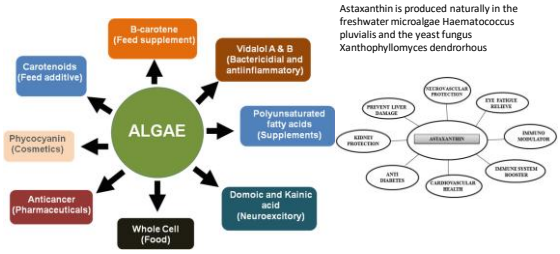
Goodies from algae



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

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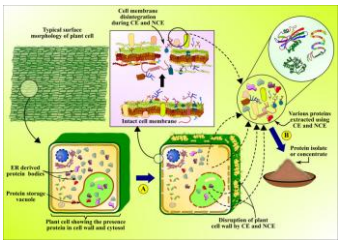
Plant protein sources, non-conventional extraction techniques (NCE)



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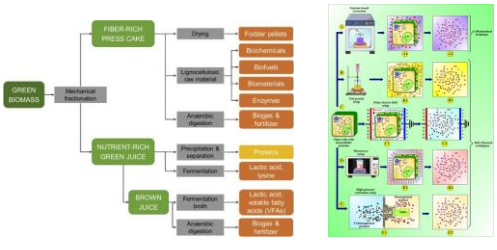
Plant protein sources, methods



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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 ?

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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

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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

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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

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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

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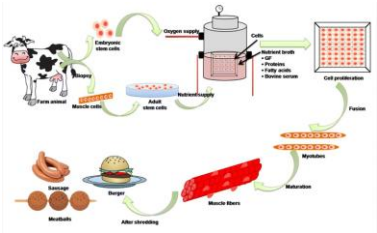
Cultured meat, production



There are three stages in the production of cultured meat.
1. Selection of starter cells,
2. Treatment of growth
3. Scaffolding,

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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.

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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.

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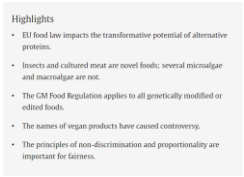
Alternative proteins EU Novel Food law and FDA



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

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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
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
Cloeotham hesperium		bacterium	Authorized novel food, only for use in food supplements	(EU) 2017/2470

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Proteins from arthropods, insects

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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/fulltext/esst-mehlwuermer,

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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]

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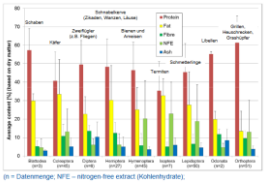
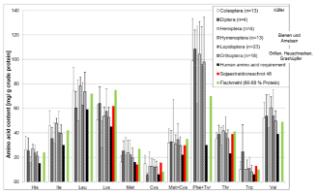
Durchschnittliche Zusammensetzung verzehrter Insekten



Aminosäurespektren verzehrter Insekten



[BfR, 2016]

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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]

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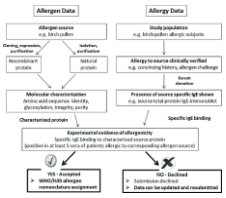
Main problem allergy in all novel protein sources



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 8 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).

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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]

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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]

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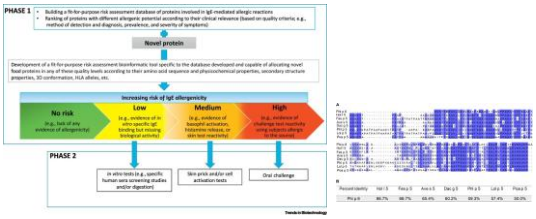

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An 80% sequence identity suggests a very high likelihood of cross-reactivity, but the standard bioinformatic criteria for assessing allergenicity are lower, with a 35% identity over 80 amino acids being the typical threshold for concern. High sequence identity like 80% indicates that two proteins are very similar, increasing the risk of a similar 3D structure and the potential for an immune system response to the new protein, but sequence identity alone is not definitive for predicting allergenicity. Therefore, a result of 80% identity would trigger additional, more rigorous testing, including experimental validation.
Standard allergenicity assessment
35% identity over 80 amino acids: This is the widely accepted threshold by organizations like the FAO/WHO and CODEX for potential allergenicity.
Six contiguous amino acids: A match of six or more consecutive identical amino acids is another criterion for potential allergenicity.
High false positive rate: While these criteria are useful, they can result in a high number of "false positives," where a protein is flagged as potentially allergenic but is not in reality.
Why 80% identity is significant
High similarity: An 80% identity means that 80% of the amino acids are identical in the same position within an alignment, indicating an extremely high level of similarity.
Structural similarity: Proteins with such high sequence identity are highly likely to have very similar three-dimensional structures, which is crucial for allergenicity. This similarity increases the chance that IgE antibodies can bind to the new protein.
Trigger for further testing: A high percentage of sequence identity, especially when compared against a short window, is often treated as a trigger for further, more complex testing, including experimental assays like IgE binding tests with patient sera.

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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]

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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]

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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)

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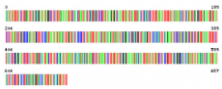
Nachweismethode Insekten

- 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]

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Lebensmittel und Nanotechnologie

Nanopartikel sind Teilchen mit mindestens einer Dimension im Bereich von ca. 1–100 nm. Durch die winzige Größe ändern sich Eigenschaften wie:

- Löslichkeit
- Reaktivität
- Oberfläche (viel größer im Verhältnis zum Volumen)

Genau diese veränderten Eigenschaften machen Nanopartikel für die Lebensmittelindustrie interessant – aber sie sind auch der Grund für Sicherheitsbedenken.

Wo werden Nanopartikel in Zusammenhang mit Ernährung eingesetzt?

Man muss unterscheiden zwischen:

1. **Direkt im Lebensmittel / Zusatzstoff**
2. **In der Verpackung**, die mit dem Lebensmittel in Kontakt steht
3. **In Nahrungsergänzung / „Functional Food"** als Träger für Vitamine, Antioxidantien usw.

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Nanopartikel als Lebensmittelzusatzstoffe

Historisch wichtiges Beispiel:

- **Titandioxid (E171)** – Weißpigment in Süßwaren, Kaugummi, Desserts, Soßen etc.
  - E171 besteht aus Mikro- und Nanopartikeln (Anteil unter 100 nm).
  - Die EFSA kam 2021 nach Neubewertung zu dem Schluss, dass E171 **nicht mehr als sicher** gelten kann (v.a. wegen möglicher Genotoxizität), und die EU hat die Verwendung als Lebensmittelzusatz untersagt.

Weitere Beispiele, die (auch) Nanogrößen enthalten können:

- **Siliciumdioxid (E551)** als Rieselhilfe in Pulvern
- einige **Farbstoffe** und **Antiklumpmittel**, bei denen ein Teil der Partikel im Nanobereich liegen kann

Für diese Stoffe wird inzwischen explizit geprüft, ob relevante Nanofraktionen vorliegen – dafür hat EFSA spezielle Leitlinien für Partikel im Nano-Bereich veröffentlicht.

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Nanotechnologie in Lebensmittelverpackungen

Beispiele für Nanomaterialien in Verpackungen:

- **Nanoclay (Nanoton)** in Kunststoffen
  → macht Folien **stabiler**, **weniger gasdurchlässig** (besserer Sauerstoff- und Aromaschutz), verlängert die Haltbarkeit.ScienceDirect+2fdbs.uni.ac.ir+2
- **Nano-Silber**
  → antimikrobiell aktiv, soll das Wachstum von Bakterien und Pilzen auf der Lebensmitteloberfläche hemmen (z.B. in Kunststoffen oder Beschichtungen).PMC+2foodstandards.gov.au+2
- **Metalloxide** (z.B. ZnO, TiO_2)
  → UV-Schutz, antimikrobiell, Verbesserung von Barriereeigenschaften.pubs.rsc.org+1

Nanoencapsulation in Functional Food & Supplements

Ein rasant wachsender Bereich ist die **Nanoverkapselung** von Nährstoffen und bioaktiven Substanzen:

- **Fettsäuren, Vitamine (z.B. D, E), Carotinoide, Polyphenole**, Probiotika usw. werden in:
  - Nanoemulsionen
  - Nanoliposomen
  - Protein- oder Polysaccharid-Nanopartikeln eingebaut.MDPI+3ScienceDirect+3PMC+3

Zweck: bessere **Löslichkeit** in Wasser, Schutz vor Licht, Sauerstoff, Hitze, **kontrollierte Freisetzung** im Darm, oft deutlich **erhöhte Bioverfügbarkeit** im Vergleich zur „normalen"Diese Systeme finden sich vor allem in:

- Nahrungsergänzungsmitteln
- angereicherten Getränken
- Sport- und Diätprodukten
  (aber häufig nicht offensiv als „Nano" beworben, u.a. wegen der kritischen öffentlichen Wahrnehmung).

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Welche Zwecke verfolgt man mit Nanopartikeln in der Ernährung?

Kurz zusammengefasst:

1. **Optik & Textur**
   - intensivere oder stabilere Farben (Pigmente)
   - cremigere Texturen, stabilere Emulsionen
2. **Konservierung & Haltbarkeit**
   - bessere Barriereverpackungen (Nanoclay, Metalloxide)
   - antimikrobielle Oberflächen (Nano-Silber)
3. **Ernährungsphysiologie**
   - höhere Bioverfügbarkeit von Vitaminen, Mineralstoffen, Pflanzenstoffen
   - „Targeting": gezielte Freisetzung im Darm
4. **Information & Qualitätssicherung**
   - „intelligente" Verpackungen mit Nanopartikeln als Sensoren (z.B. Farbänderung bei Verderb, Gassensoren).PMC+2pubs.rsc.org+2

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Gesundheitsrisiken:

4.1. Allgemeine Problempunkte bei Nanopartikeln

- **Größe & Oberfläche**: Kleine Partikel können biologische Barrieren (Darm, ggf. Blut-Gewebe-Barrieren) einfacher überwinden.
- **Unlösliche / biopersistente Partikel** (z.B. Titandioxid, Metalloxide) können sich im Körper anreichern.
- **Reaktive Oberflächen** können oxidativen Stress und Entzündungsprozesse auslösen.
- **Genotoxizität**: Manche Nanopartikel könnten DNA schädigen (direkt oder indirekt über ROS).

Das Problem: Toxikologische Standardtests sind ursprünglich für „normale" Chemikalien gemacht, nicht für Nanomaterialien – deshalb hat EFSA eigene Leitlinien für die Risikobewertung von Nanomaterialien in der Nahrungskette entwickelt.

4.2. Beispiel Titandioxid (E171)

Warum verboten?

- Ein signifikanter Teil der Partikel in E171 liegt im Nanobereich.
- In Tier- und Zellstudien wurden Hinweise auf:
  - **DNA-Schäden**
  - chromosomale Aberrationen
    gefunden.
- EFSA konnte keine **sichere Aufnahmemenge (ADI)** mehr ableiten, weil ein mögliches genotoxisches Risiko nicht ausgeschlossen werden konnte – und bei Genotoxizität gibt es per Definition keinen „Unbedenklichkeitsschwellenwert".

Daher die Bewertung: **„nicht mehr als sicher anzusehen"**, was faktisch zum Aus für E171 in Lebensmitteln in der EU geführt hat.

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Gesundheitsrisiken durch Nanopartikel aus Verpackungen

Die Frage ist hier: **Wie viel wandert überhaupt ins Lebensmittel?**

- Studien zu **Nanoclay** in PET-Kunststoffen zeigen häufig **keine oder extrem geringe Migration** ins Lebensmittel.
- Bei **Nano-Silber-Kunststoffen** wurden in einzelnen Untersuchungen **geringe Mengen Silber** im Lebensmittel nachgewiesen, aber deutlich unter toxikologisch relevanten Schwellen

Risiken, über die diskutiert wird:

- mögliche **Störung des Darmmikrobioms** durch antimikrobielle Metalle (Silber, Kupfer)
- mögliche **Bioakkumulation** in Organen bei wiederholter Aufnahme
- unsichere Langzeitwirkungen (viele Studien sind kurz- bis mittelfristig).PMC+1

Der aktuelle Stand vieler Behörden:

Bei **heute zugelassenen** nano-basierten Verpackungsmaterialien sind die erwarteten Expositionen **sehr niedrig**, aber es wird betont, dass die Langzeitrisiken weiter erforscht werden müssen

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Nanosilber

2.1. Antimikrobielle Wirkung

Nanosilber ist eines der effektivsten bekannten antimikrobiellen Nanomaterialien und wirkt gegen: Bakterien (Gram+ und Gram−), Pilze, Viren (bei einigen Studien nachgewiesen)

Mechanismen:

- Freisetzung von Silberionen (Ag^+), die für Mikroorganismen toxisch sind, Bindung an bakterielle Zellwände → Strukturzerstörung, Bildung reaktiver Sauerstoffspezies (ROS)
- Hemmung bakterieller Enzyme und DNA-Replikation

Darum ist nanoskaliges Silber **10–100× wirksamer** als großformatiges Silber.

Typische Anwendungen (mit Bezug zur Ernährung)

a) Lebensmittelverpackungen

- In Kunststoffen und Folien zur **Hemmung von Bakterienwachstum** an der Oberfläche
- Ziel: **Längere Haltbarkeit**, weniger Verderb
- Anwendung häufig in:, Schneidebrettern, Lebensmittelbehältern, Frischhaltefolien, Kühlschrankbeschichtungen

b) Oberflächen in Lebensmittelverarbeitung

- Beschichtungen von Produktionsanlagen, antimikrobielle Arbeitsflächen

Zweck: **Reduktion von Kontaminationen**, hygienischere Verarbeitung.

c) Verbraucherprodukte

- angeblich „antibakterielle" Küchenschwämme, Textilien, Kühlschränke

Silber-Nanopartikel werden **in der EU bisher nicht als Lebensmittelzusatzstoff** zugelassen. Sie dürfen also nicht direkt ins Lebensmittel eingemischt werden.

teilweise umstritten und nicht immer reguliert.

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Risikobewertung von Nanosilber

Die Risikobewertung ist komplex, da **Nanosilber sowohl Silberionen freisetzt (chemische Toxizität)** als auch **nanomaterialtypische Risiken** besitzt.

3.1. Aufnahmewege

Für Verbraucher:

- orale Aufnahme durch Lebensmittelkontaktmaterialien
- dermal (Hautkontakt mit Textilien etc.)
- inhalativ (Aerosole, techn. Anwendungen)

Für Ernährung relevant: **orale Exposition** durch Migration aus Verpackungen.

Migrationspotenzial in Lebensmittel

Studien zeigen:

- Bei gut eingebetteten Nano-Silberpartikeln in Polymermatrices (PE, PP, PET) findet meist **sehr geringe bis kaum messbare Migration** statt.
- In einigen Fällen jedoch Migration von **Silberionen** in Lebensmittel, besonders bei:
  - Kontakt mit sauren Lebensmitteln
  - Lagerung über lange Zeit
  - hohen Temperaturen
  - minderwertigen / schlecht stabilisierten Materialien

Grundregel:
Je besser die Partikel im Kunststoff fixiert sind, desto geringer die Migration.

Die meisten Behörden sehen bei heutigen Anwendungen eine **geringe, aber nicht völlig geklärte Exposition**.

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Toxikologische Aspekte von Nanosilber

a) Silberionen-Toxizität (gut untersucht)

Silberionen können bewirken: Mitochondriale Schäden, Hemmung von Enzymen, oxidative Stressreaktionen

Chronisch hohe Aufnahme kann zu **Argyrie** führen (grau-bläuliche Hautverfärbung, bei extrem hohen Mengen). Diese Mengen werden durch Lebensmittelkontakt aber **nicht annähernd erreicht**.

b) Spezifische Risiken von Nanosilber (Nanopartikel-Effekte)

Nicht vollständig geklärt, aber Hinweise auf: **Zellstress & oxidative Schäden**, **DNA-Schädigung** in In-vitro-Studien, mögliche **Einlagerung** in Leber, Milz, Niere

mögliche Auswirkungen auf das **Darmmikrobiom** Hemmung „guter" Darmbakterien schon bei niedriger Konzentration

Tierstudien zeigen, dass Silber-NP im Körper **langsamer ausgeschieden** werden als Silberionen.

EU (EFSA, ECHA, SCENIHR)

- EFSA hat **keine Zulassung** für Nanosilber als Lebensmittelzusatz oder „active substance" in direktem Kontakt mit Lebensmitteln erteilt.
- Für Lebensmittelkontaktmaterialien wird Nanosilber **nicht grundsätzlich verboten**, aber es muss nachgewiesen werden, dass:
- keine nennenswerte Migration erfolgt, und, keine toxikologisch relevanten Mengen aufgenommen werden. ECHA klassifiziert einige Silbernanopartikel als **umweltgefährlich**, v.a. durch Wirkung auf aquatische Organismen.

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Nanoencapsulation von Nährstoffen / bioaktiven Stoffen

Potenzielle Vorteile:

- Bessere Aufnahme kann theoretisch sogar **gesundheitsfördernd** sein (z.B. bessere Versorgung mit Vitamin D, Omega-3, Antioxidantien).
- Man braucht evtl. **geringere Dosen**, um denselben Effekt zu erzielen. **Mögliche Risiken:**
- Höhere Bioverfügbarkeit bedeutet auch:
  - stärkere **systemische Exposition** des Körpers
  - mögliche **Überdosierung**, wenn Produkte falsch eingesetzt werden.
- Die **Trägermaterialien** (z.B. synthetische Polymere, bestimmte Lipide, anorganische Nanopartikel) können eigene toxikologische Profile haben.
- Unklar ist häufig:
  - verändern nanoverkapselte Stoffe das **Verteilungsmuster im Körper**?
  - gelangen sie leichter in empfindliche Organe (Leber, Gehirn, Plazenta)?

Regulatorisch gilt in der EU:
Lebensmittel mit **„engineered nanomaterials"** gelten in der Regel als **Novel Food** und benötigen eine eigene Sicherheitsbewertung, bevor sie zugelassen werden.

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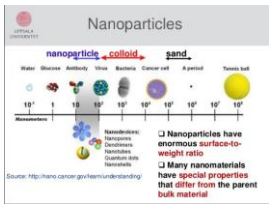
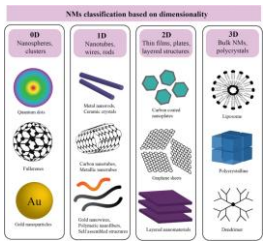
NANO particles, nutrition and foods





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

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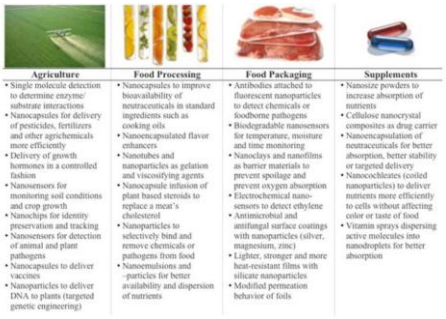

Agriculture	Food Processing	Food Packaging	Supplements
• Single molecule detection to determine enzyme/ substrate interactions • Nanocapsules for delivery of pesticides, fertilizers and other agrichemicals more efficiently • Delivery of growth hormones in a controlled fashion • Nanosensors for monitoring 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 • Nanoochlerates (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

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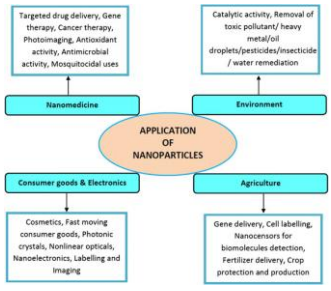

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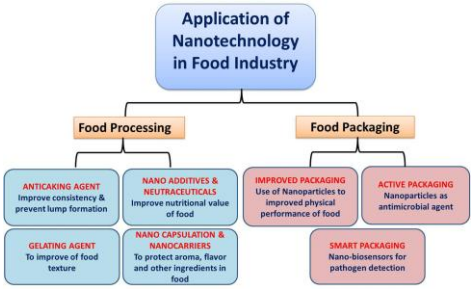

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Nanoparticles: Delivery, stability, release

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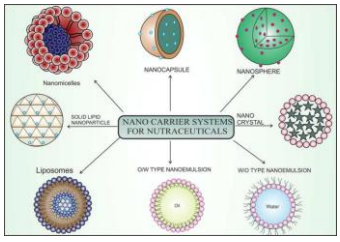
Nano carriers



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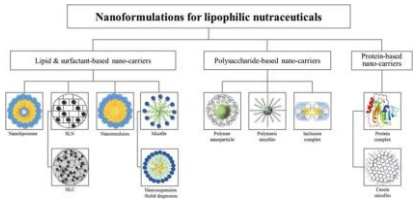
Nano and nutraceuticals



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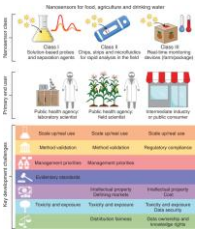
Nano sensors



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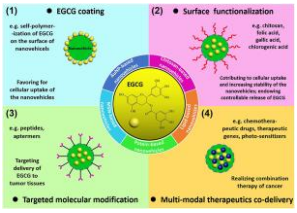
Nutraceuticals delivery



Gold nanoparticles , GNPs

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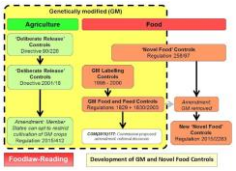
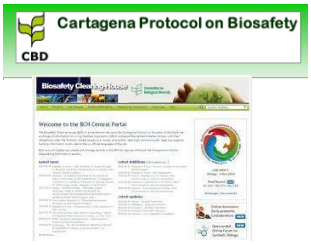
Developments novel food regulation, vertical, horizontal





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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.

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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

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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*)

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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.

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On the market before 15 May 1997, consequences

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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).

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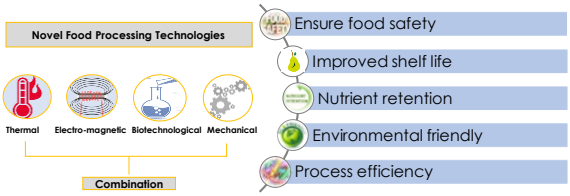
Novel foods because of processing technologies



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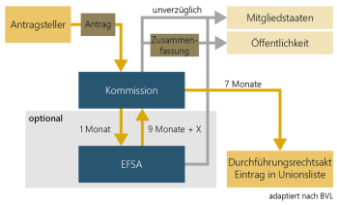
Authorisation process



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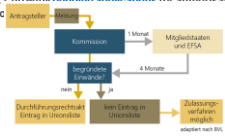
Notification of a traditional food from third countries

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 cc ı Commission.



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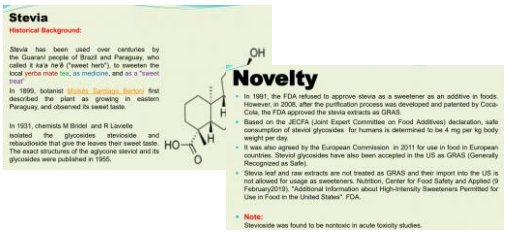
Examples, Stevia



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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.**

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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 Verzehrmengen akzeptabel ist.
- Die EFSA hat am 8. 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 Verzehrmengen unerwünschte Nebenwirkungen auf die menschliche Leber auslösen könnte.

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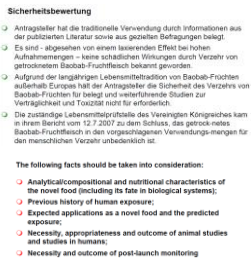
Baobab



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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.

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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)

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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)

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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 (Tenaka 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"

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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)

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Points to consider

- 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)?

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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.*"

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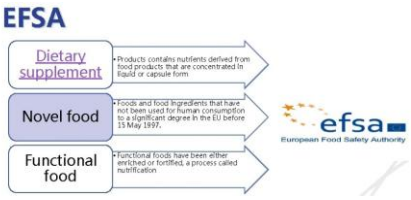
Supplements, NF, functional foods



Nutraceuticals, Botanicals
Foods for special medical purposes

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Supplements,Food improvements

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Safe food additives. Relevant For a lifetime daily consumption ?

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.

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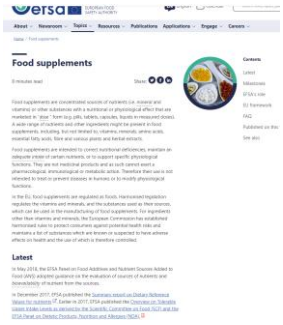
Supplements , EU upper intake levels



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Supplements , EFSA

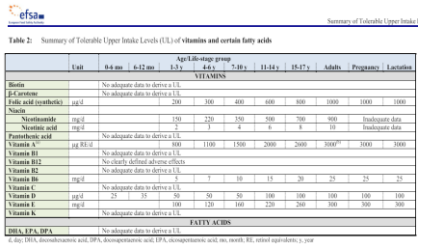

Table 2: Summary of Tolerable Upper Intake Levels (ULs) of vitamins and certain fatty acids

	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			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; DPA, docosapentaenoic acid; mo, month; RE, retinol equivalents; y, year

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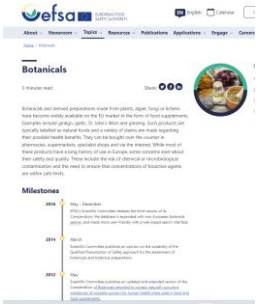
Botanicals EU



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Foods for special medical purposes

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

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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.

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Nutraceuticals, Botanicals , EU

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 2008, 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.

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Example, botanical

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

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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.

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Catechins and regulations

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.

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Examples of Functional Foods Approved as EU Novel Foods

Novel Food / Ingredient	Typical Functional Use	Approved Forms / Notes
Chia seeds (*Salvia hispanica*)	Omega-3, fibre enrichment	Bread, cereals, yogurts, juices
Algal oil (DHA/EPA)	Brain & heart–support functional products	DHA/EPA-rich oils from *Schizochytrium*, *Ulkenia*, *Nannochloropsis*
Phytosterols / Phytostanols	Cholesterol-lowering foods	Spreads, yogurt drinks, dairy products
Noni juice (*Morinda citrifolia*)	Antioxidant-rich beverages	Allowed in drinks and concentrates
Baobab fruit pulp	Vitamin- and fibre-rich functional drinks	Smoothies, bars, beverages
Red yeast rice (Monacolin K)	Cholesterol-management supplements	Strict conditions due to safety concerns
Krill oil (Antarctic krill)	Omega-3 functional supplements	Capsules, oils
Bovine lactoferrin	Immune- and gut-health functional dairy	Infant formula, yogurts, drinks
Stevia (steviol glycosides)	Sugar reduction / functional beverages	Approved sweetener from stevia leaves
Yarrowia lipolytica yeast biomass	Protein and B-vitamin enrichment	Bakery, bars, meat alternatives
Insect proteins (e.g., *Acheta domesticus*, *Locusta migratoria*, *Alphitobius diaperinus*)	High-protein functional foods	Bars, pasta, snacks, bakery
Fucoidan extract (brown algae)	Functional drinks, immune-focused products	Extract in beverages & supplements
Coffee berry extract (cascara)	Natural caffeine / antioxidant drinks	Functional beverages & shots

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Kennzeichnung claims Regional differences

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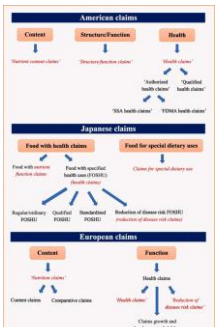
Regional differences



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Health claim regulation, EU: Klassifikation von Claims

A. Nährwertbezogene Angaben (Nutrition Claims)

Beziehen sich auf die **Eigenschaft eines Lebensmittels**, z. B.:

- „fettarm", reich an Vitamin C"„zuckerfrei" „proteinreich"
  Muss einer **abgeschlossenen Liste zulässiger Angaben (Anhang der Verordnung)** entsprechen. Frei formulieren ist nicht erlaubt.
- **B. Allgemeine gesundheitsbezogene Angaben (Health Claims – Article 13)**

  Beschreiben **allgemeine physiologische Wirkungen**:
- „Kalzium wird für die Erhaltung normaler Knochen benötigt"
- „Ballaststoffe unterstützen die Verdauung"

  Werden auch „Function Claims" genannt.

Nur zulässig, wenn von der **EU scientific database** genehmigt.

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C. Krankheitsbezogene Angaben (Article 14 Claims)

1. Risikoreduktionsclaims

- z. B. „Pflanzensterine senken nachweislich den Cholesterinspiegel. Ein hoher Cholesterinspiegel ist ein Risikofaktor für Herzkrankheiten."

2. Claims über die Entwicklung und Gesundheit von Kindern

- z. B. „DHA trägt zur normalen Gehirnentwicklung von Kindern bei."

Erfordern ein *vollständiges* Zulassungsverfahren durch **EFSA** (European Food Safety Authority) + Zustimmung der Kommission.

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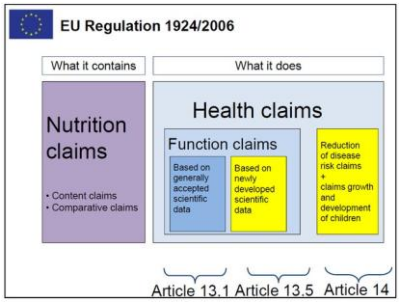
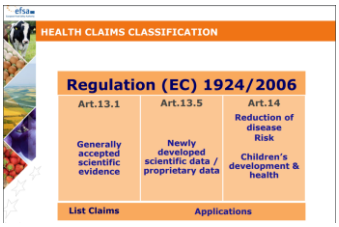


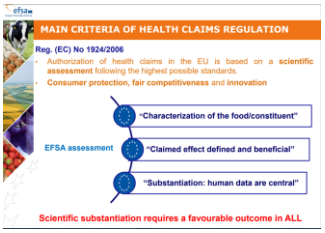
382

Health claim classification



383

Health claim regulation, EU EFSA



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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)

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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

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Examples of accepted and non accepted EU health claims (Article 13)

✓ ACCEPTED	NON-ACCEPTED
• Vitamin C contributes to the reduction of tiredness and fatigue	• Boosts your energy levels
• Calcium is needed for the maintenance of normal bones	• Strengthens bones
• Fiber supports normal bowel function	• Improves digestion

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Examples of accepted and non accepted EU health claims (Article 14)

✓ ACCEPTED	NON-ACCEPTED
• Plant sterols have been shown to lower/ reduce blood cholesterol. Blood cholesterol is a risk factor in the develop-ment of coronary heart disease	• Reduces the risk of heart attack • Helps prevent vision problems in infants

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Examples of Functional Foods with Claims Not Accepted by the EU

. Probiotic drinks (general claims)

•Non-accepted claims:
"Boosts immunity," "improves gut health," "supports digestive balance."
→ Rejected because claims were vague, not measurable, or not proven.
2. Antioxidant-rich products (e.g., berry juices, extracts)
•Non-accepted claims:
"High antioxidants protect against aging," "neutralizes free radicals," "supports healthy cells."
→ Most antioxidant claims were rejected for lack of proven clinical effect.
3. Collagen-enriched functional beverages
•Non-accepted claims:
"Reduces wrinkles," "improves skin elasticity," "rebuilds joints."
→ Rejected due to insufficient human evidence.
4. Green tea extract drinks
•Non-accepted claims:
"Promotes weight loss," "boosts metabolism," "burns fat."
→ EFSA concluded the effect was not sufficiently substantiated.
5. Cranberry functional juices
•Non-accepted claims:
"Prevents urinary tract infections."
→ Rejected due to insufficient proof of cause-effect in humans.

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Accepted, non accepted in health claim regulation

Functional Food	Example Accepted Claim	Example Non-Accepted Claim
Yogurt with cultures	Improves lactose digestion	"Boosts gut health"
Plant sterol margarine	Lowers blood cholesterol	"Prevents heart attack"
Oat β-glucan products	Maintains normal cholesterol	"Reduces heart disease risk"
Fish/Algal DHA products	Supports normal heart function	"Improves memory"
Cranberry juice	–	"Prevents UTIs"
Probiotic drinks	(Only lactose claim accepted)	"Strengthens immune system"
Collagen drinks	–	"Reduces wrinkles"

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Problems of gut immune claims

No "probiotics", "prebiotics", or "postbiotics" have approved health claims in the EU — with ONE narrow exception.
Accepted (Article 13):"Live cultures in yogurt improve lactose digestion of the product in individuals who have difficulty digesting lactose." ➡ Applies only to Lactobacillus delbrueckii subsp. bulgaricus and Streptococcus thermophilus. ➡ It is NOT a general "probiotic" health claim. ❌

Rejected or not authorised claims:"Supports immunity""Promotes healthy gut flora""Improves digestion""Strengthens natural defenses"Any strain-specific claims (e.g., L. rhamnosus GG, B. infantis)Reason: EFSA repeatedly concluded insufficient cause–effect evidence. ☑️ 2. PREBIOTICS — Accepted?No prebiotic-specific claims are authorised.This includes inulin, FOS, GOS, XOS, etc.However, certain fibres have accepted claims when they act via physiological effects, not as "prebiotics".✓Accepted (but not because they are prebiotics):Wheat bran fibre: "Contributes to intestinal transit."Beta-glucan (oats, barley): "Helps maintain normal blood cholesterol levels."Chicory inulin-type fructans: Claims have not been accepted as prebiotics. ❌ Rejected claims:"Feeds good bacteria""Supports microbiome balance""Improves gut health via prebiotic effect" ❌ 3. POSTBIOTICS — Accepted?No postbiotic-related health claims are accepted in the EU.(E.g., heat-killed bacteria, metabolites, engineered fermentation products)Examples of rejected/unauthorised claims:"Strengthens immune system""Reduces inflammation""Improves gut barrier function"EFSA has not approved any postbiotic as having a cause–effect relationship for a health benefit. 4. Why no claims?EFSA's main arguments in rejections: Lack of strain-specific evidenceStudies too heterogeneousunclear mechanisms insufficient human RCTsuse of non-authorised terminology ("probiotic" considered a health claim by itself) ⭐

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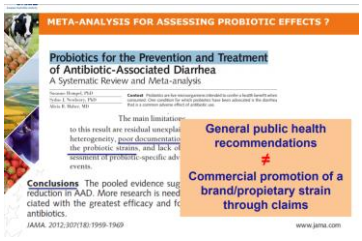
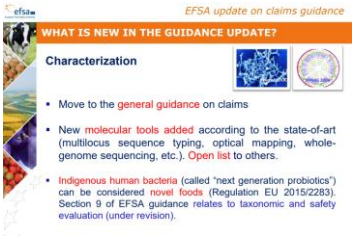
Really no evidences ?



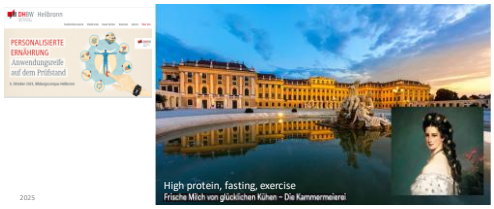
392

New developmements



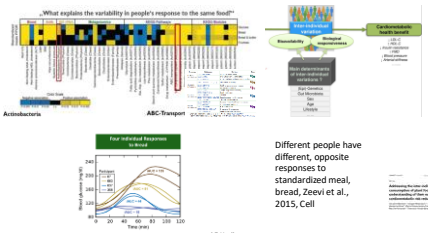
393

Personalisation and novel foods



394

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

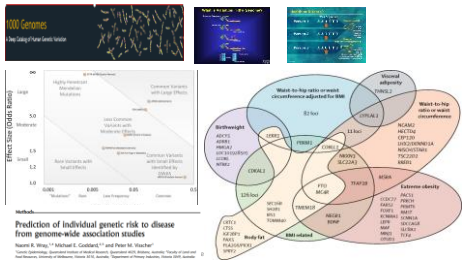


Different people have different, opposite responses to standardized meal, bread, Zeevi et al., 2015, Cell

395

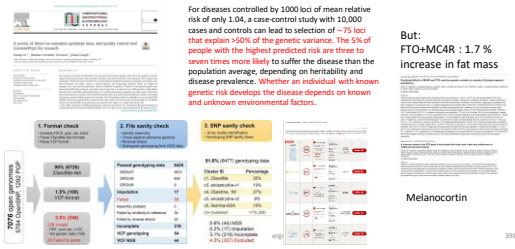
396

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



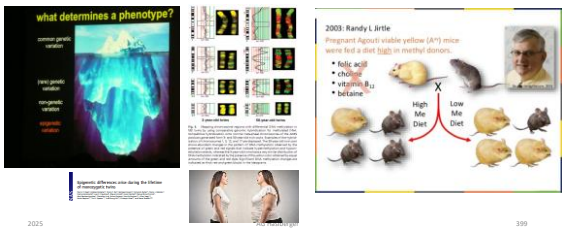
397

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



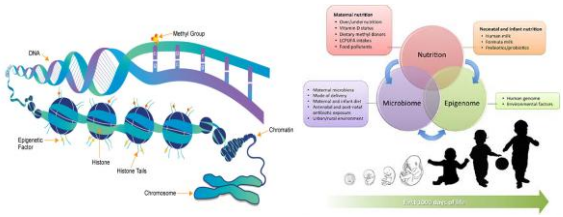
398

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



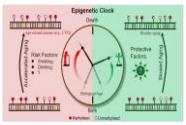
399

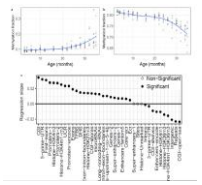
Epigenetics mechanisms, Interactions, early imprinting



400

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

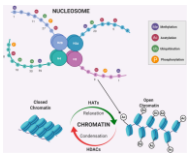




Intrinsic age: Horvath
multiple tissues.
Extrinsic Hannum,
blood cell

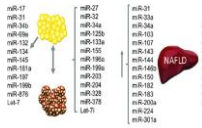
401

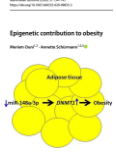
Nutrition: central importance Epigenetic histone-mediated regulation: e.g. C.R. regulate sirts, (HDACs; do all benefit from a SIRT diet ?



402

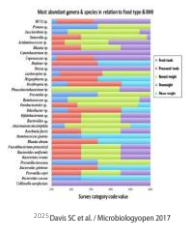
Epigenetic miRNAs: food borne and regulators and markers of metabolic mechanisms, phenotypes, disorders

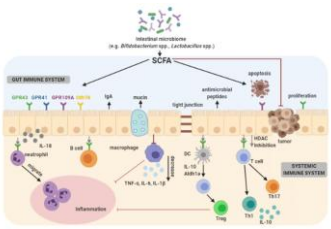




403

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

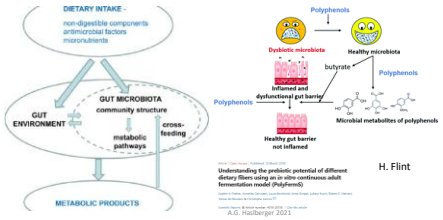




 Davis SC et al. / Microbiologyopen 2017

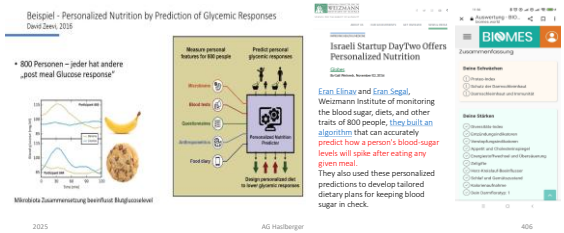
404

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



405

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



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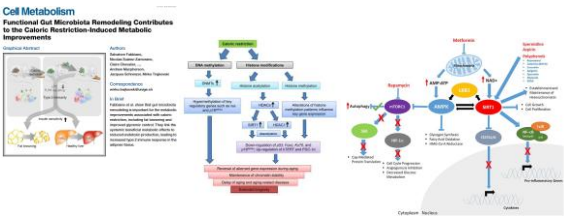
So, Genetic and microbiota analysis for personal dietary plans, But of central importance are Interactions microbiota with epigenetic System; host gut interactions e.g. in C.R., Fasting (fasting Mimetics)



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Ageotype	Typische Merkmale	Biologische Mechanismen	Wichtige Marker
Metabolisch	Insulinresistenz, viszerales Fett	Nutrient-Sensing, Mitochondrien	Glukose, HbA1c, TG/HDL
Immun/Entzündung	Infektanfälligkeit, CRP↑	Inflammaging, Immunseneszenz	hsCRP, IL-6, TNF-α
Mikrobiom	Dysbiose, Verdauungsprobleme	Barriere-Störung, SCFA↓	Diversität, Endotoxine
Hepatisch	Fettleber, Enzyme↑	Proteostase, Detox	ALT, AST, GGT
Renal	eGFR↓, Kreatinin↑	Stammzell-Erschöpfung	Kreatinin, Albuminurie
Mitochondrial	Erschöpfung, VO_2max↓	ATP-Verlust, ROS↑	VO_2max, mtDNA
Epigenetisch	DNAmAge↑	Methylierung, Genexpression	DNAmAge, Telomere
Vaskulär	Bluthochdruck	Endothelaltetung	PWV, Blutdruck

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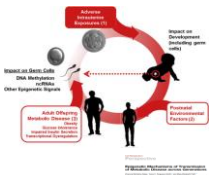
Conclusion: Complex diseases (Aging) can arise from (a mixture of) personal diverse causes, an argument in favor of personally specific interventions (e.g. metabolic disease)



		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		

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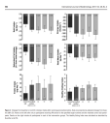
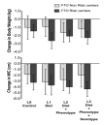
Consequences for Intervention: Flagship EU-Food4me study results prove „personal nutrition does better than on size fits all“, J. Mathers



Chango of dietary intake after personalised advice
Healthy eating index



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

2025 AG Hasiberger 410

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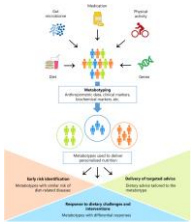
Definition of metabotypes from genetic-, microbiota-metabolomics based information, Metabotyping



Molecular Nutrition & Food Research

Evaluation of the Metabotype Concept Identified in an Irish Population in the German KORA Cohort Study

Optimisation of a metabotype approach to deliver targeted dietary advice

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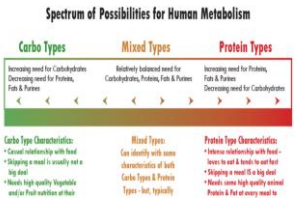
Consequences of Metabotypes, diets next step trackers



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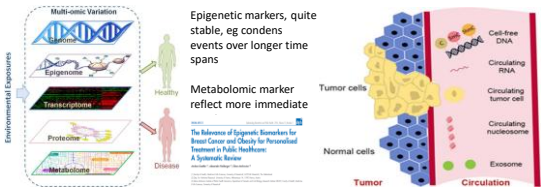
Personalisation of additives for Prevention
Monitoring basic hallmarks of health/aging. Use of mixes of supplements, functional foods which address specific mechanisms „Achilles Fersen Concept“

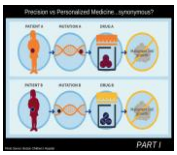
413

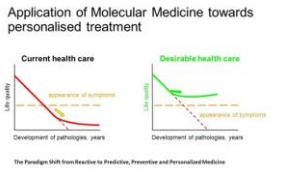
Importance of good Markers, Nutrition: following the way of personalised, prezision medicine, CFDNA ?



414

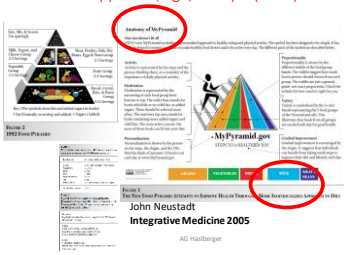
Prevention, intervention, Salutogenesis
personal or precision medicine, synonyme?
personal or precision nutrition, synonyme?





415

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



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

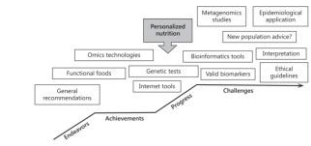

Fig. Achievements already made and challenges faced by personalised nutrition (Prasad et al., 2016)

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

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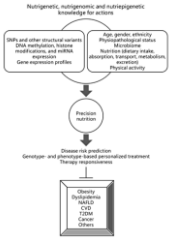
Precision-, personalised nutrition, the way we may go



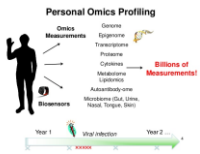
Mobile apps and wearable devices facilitate real-time assessment of dietary intake and provide feedback which can improve glycaemic control and diabetes management.

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).

418

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



419

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

www.my-personal.health

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