Novel Foods
Haslberger WS 2023

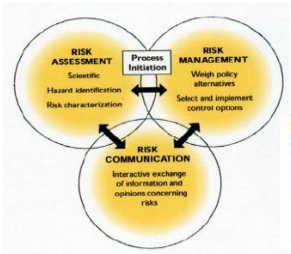
- Development in breeding and biotech
- GVOs, CRISPR
- Cloning and epigenetics
- Foods, microbiota, the I,S. and epigenetics, aging
- Functional foods, pro, pre, syn, post biotics
- Nutraceuticals , medicinal foods
- Fermenting foods, meat
- Foods from new technologies
- Ethnic foods
- Nano in food industry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

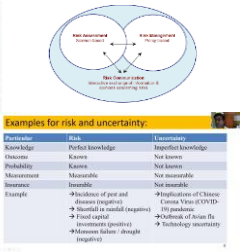
1

Materials

2

WHO , UN, Risk Assessment





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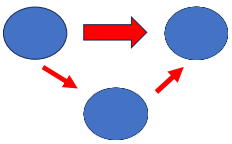
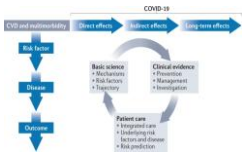
Direct, indirect risk, (long term) Epidemiologie





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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.

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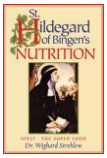
Nutrition, Foods , Health

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"**



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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

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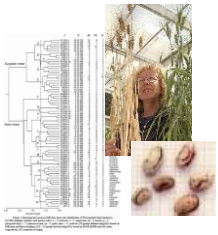
Landraces, Diversity

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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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)

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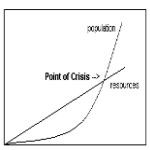
T. Malthus: 1766- 1834
Crisis in food production



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

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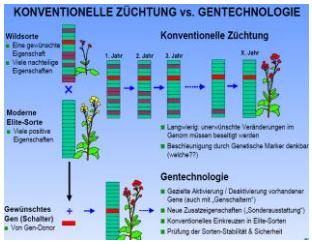
Pflanzenzüchtung
Breeding, yield, time for development



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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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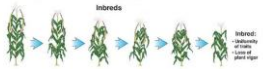
Hybridzüchtung, Heterosis

- 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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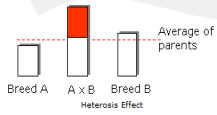
Hybrid: Heterosis effect

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	Above	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 Petite	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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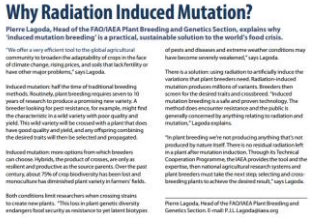
IAEA



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.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 J22, 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. seedlessness) 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, *Nelspruit*. Contact Mrs Iris Human at E-mail: iris@itsc.agric.za to order a copy of the article.

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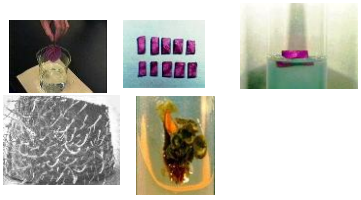
Tissue culture , Clones ?



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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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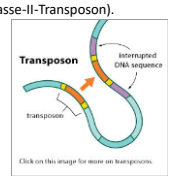
Breeding using transposons

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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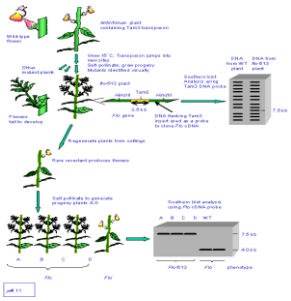

Transposon tagging

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

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Molecular marker directed breeding

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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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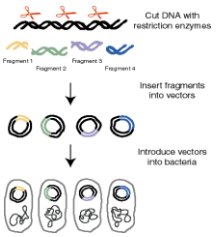
DNA cloning:



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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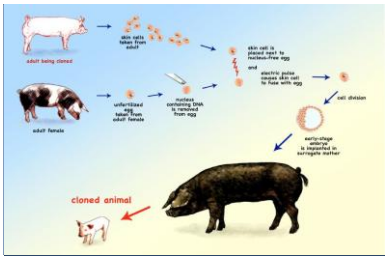
Reproductive Cloning



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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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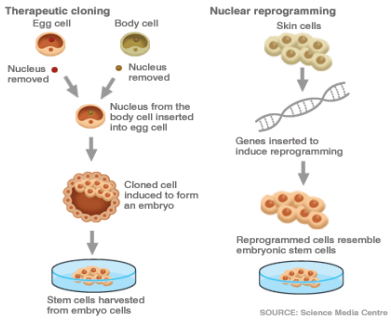

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Horticultural cloning

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.

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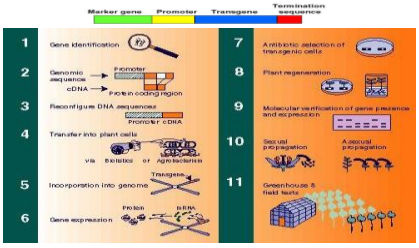
GM plants, Tranferring traits in ways which are not used in nature: GMOs



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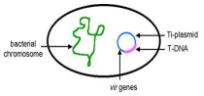
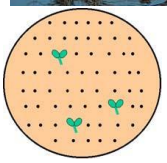
Agrobact. tumefaciens





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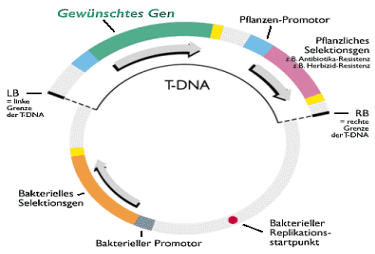
T DNA



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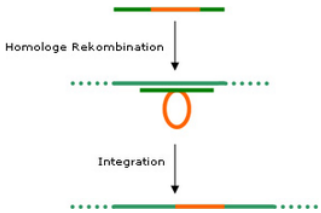
Homologic recombination



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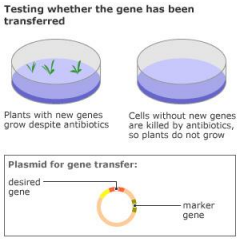
Antibiotic resistance marker gene



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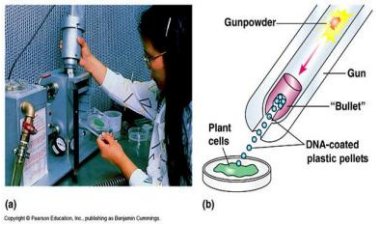
Gene gun



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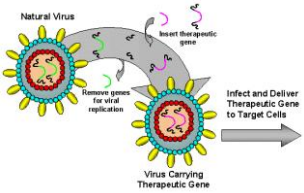
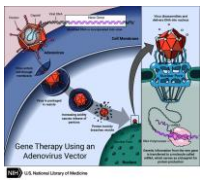
Gene transfer with viruses





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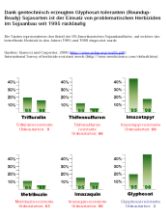
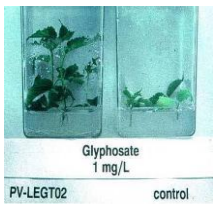
Main GMOs, Herbicide tolerance, glyphosate





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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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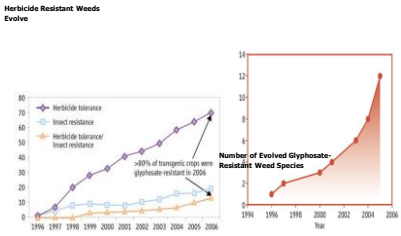
Old and new Problems: Resistance



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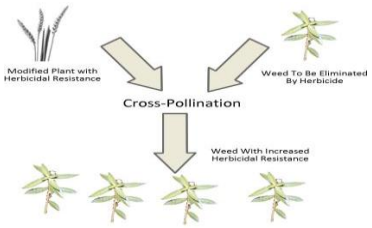
Herbizide resistance, gene transfer



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Gene flow: multiresistant Rape

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, 110-0005, 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, 62 B. rapa and 263 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 setup of oilseed rape has not been developed and distributed for commercial purposes. As found in this study, it is necessary to lengthen investigations of B. rapa and 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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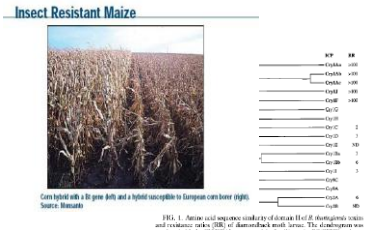
BT resistance: B. thuringiensis proteins



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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.

55

GMO tobacco, expression of human proteins in plants

56

GMOs in development:
CLAIMED BREEDING OBJECTIVES

152

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CLAIMED BREEDING OBJECTIVES

153

58

09.12.2008

Claimed breeding objectives

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BREEDING OBJECTIVES

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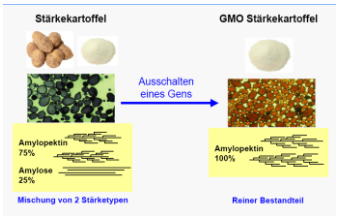
Breeding objectives



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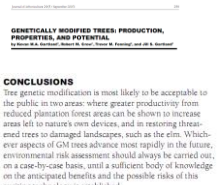
GMO Trees



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.

62

GM FLowers

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

Source: DailyTech • October 30, 2009

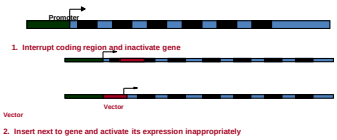
A rather unusual way of rectifying manufacturing emissions has been developed by the world's leading automaker.

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.

63

Safety: Random integration, Insertional mutagenesis



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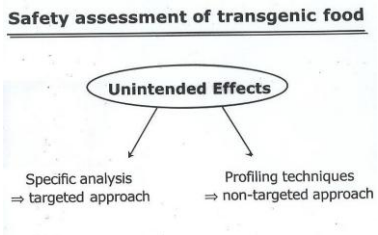

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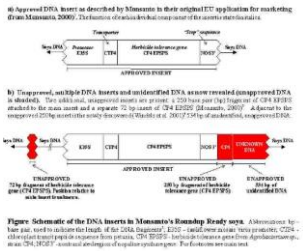

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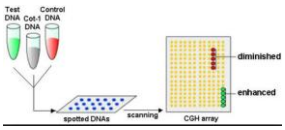
Toxicology Asessment: Difficulties Animal Feeding Studies Whole Foods

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

67

Detection of unintended effects in vitro, in vivo



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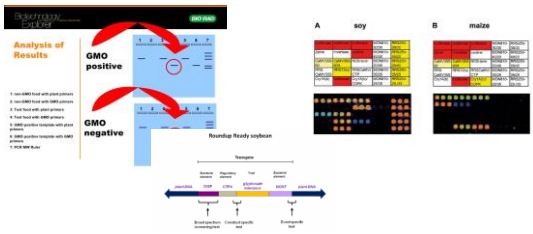
GMO tests: PCR, primers, areas, array



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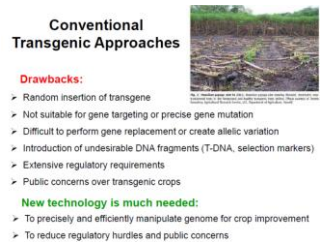
New Objectives for gene transfer



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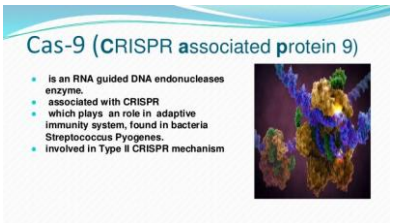
Gene editing



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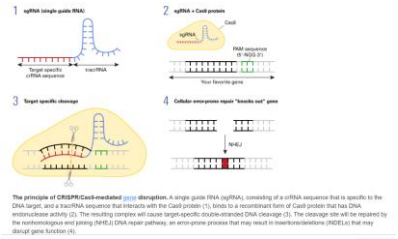

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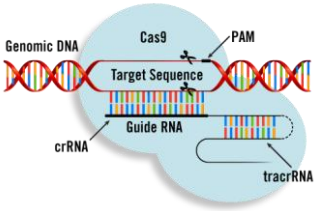
CRISPR/CAS9



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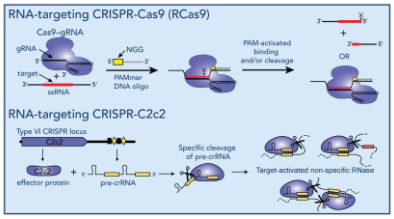
Targeting RNA



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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*

Rice Variety	Resistant with AVR-Pita Fungus	Rice Type	Amino Acid Position 147	148	150	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
Tsuyuake	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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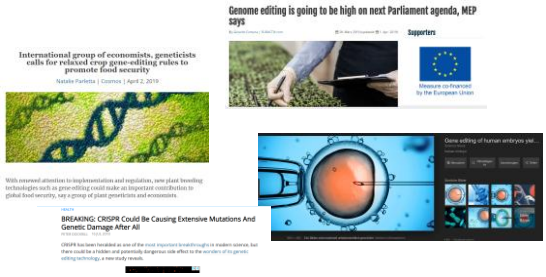

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Novel food, functional food, pro-, pre-, syn-, postbiotics

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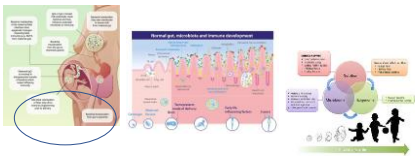
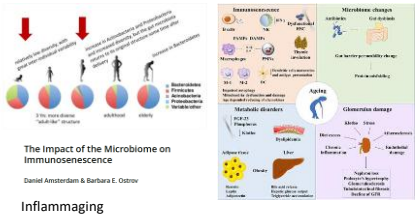
Development of microbiota, I.s., and epigenetic system, imprinting



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

80

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



Inflammaging

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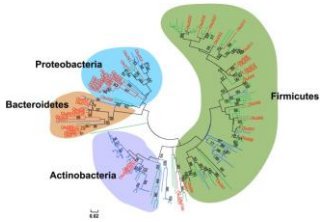
Structure microbiota



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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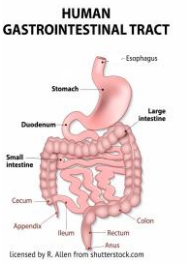
GI Microbiota

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

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



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

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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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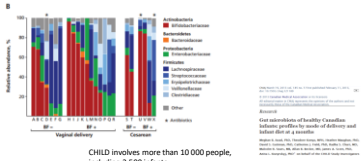
Ways of delivery and microbiota: a long lasting difference

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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We are not born sterile !

HHS Public Access

Author manuscript

Author Manuscript, available in PMC 2018 August 01.

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The prenatal gut microbiome: Are we colonized with bacteria in utero?

Ryan W Walker[1], Jose C Clemente[2], Inga Peter[3], and Ruth JF Loos[4]

[1]Preventive Medicine, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

[2]Genetics and Genomic Sciences, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Abstract

The colonization of the gut with microbes in early life is critical to the developing newborn immune system, metabolic function and potentially future health. Maternal microbes are transmitted to offspring during childbirth, representing a key step in the colonization of the infant gut. Studies of infant meconium suggest that bacteria are present in the fetal gut prior to birth, meaning that colonization could occur prenatally. Animal studies have shown that prenatal transmission of microbes to the fetus is possible and physiological changes observed in pregnant mothers indicate that in utero transfer is likely in humans as well. However, direct evidence of in utero transfer of bacteria in humans is lacking. Understanding the timing and mechanisms involved in the first colonization of the human gut is critical to a comprehensive understanding of the early life gut microbiome. This review will discuss the evidence supporting in utero transmission of microbes from mother to infants. We also review sources of transferred bacteria, physiological mechanisms of transfer and modifiers of maternal microbiomes and their potential role in early life infant health. Well-designed longitudinal birth studies that account for established confounders of the gut microbiome are challenging, but will be necessary to confirm in utero transfer and further our knowledge of the prenatal microbiome.

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GI microbiota: Diversity of groups and functions important for health

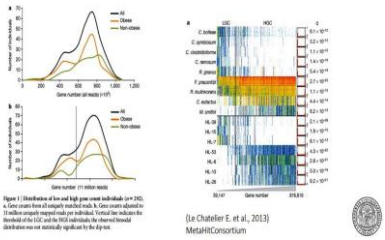

Figure 1 | Distribution of low and high gene count individuals (n= 243). a, Gene counts from all uniquely matched reads. b, Gene counts adjusted to 11 million uniquely mapped reads per individual. Vertical line indicates the threshold of the LGC and the HGC individuals; the observed bimodal distribution was not statistically significant by the dip test.

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

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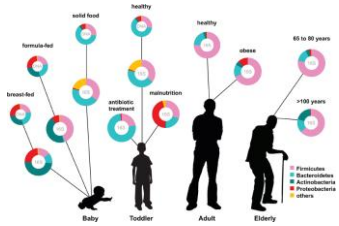
Aging and Microbiota



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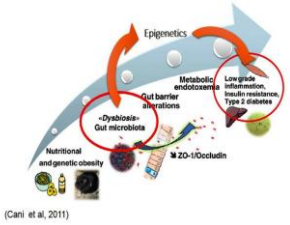
Bacterial cell wall components and Inflammation: dysbiosis, LPS and gut permeability; obesity as a model



(Cani et al, 2011)

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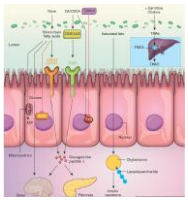
Endotoxins, saturated fats/ chylomicrons trigger inflammation, insulin resistance; SCFAs may trigger GLP1 activation

GLP1: incretin improves DMII and obesity



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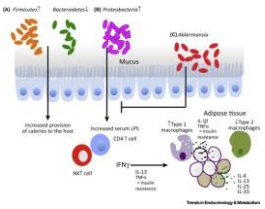
Obesity: Firmicutes: Bacteroidetes; Akkermansia and the cell wall



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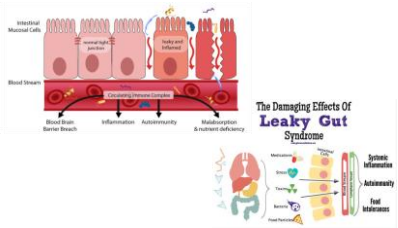
leaky gut: a major health problem



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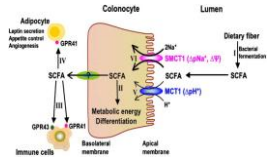
Microbiota metabolites: SCFAs bind to G-Protein-Receptors GPR 41/43 (FFARs)



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 (Ruminococcaceae)	*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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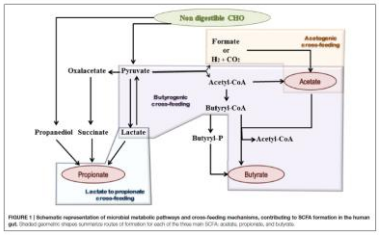
Pathways and cross feeding for SCFAs/ Butyrate



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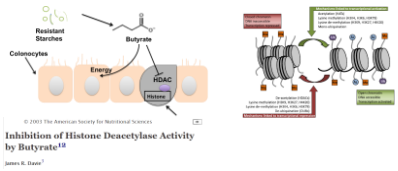
Butyrate and epigenetic histone modulation



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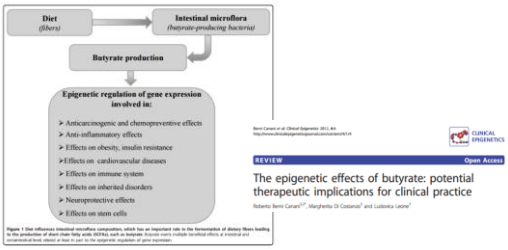
Butyrate and epigenetics



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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, Alli/ald0 (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 hyperacetylator

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

Karen S Bishop[1], Hussean Xu[2] and Gareth Marlow[3]

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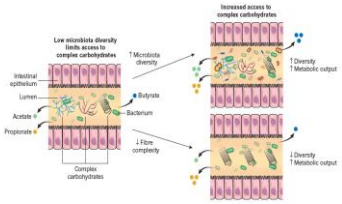
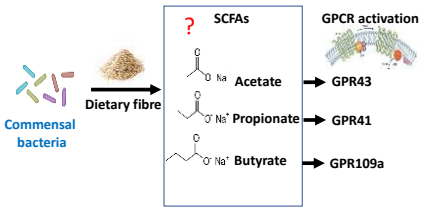
Diet dictates the production of SCFAs, diversity of the microbiota, many types of complex carbs



100

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

- SCFAs are major metabolites produced by the microbiota



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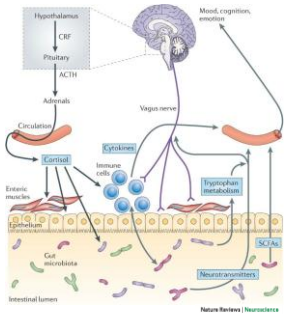
Gut-Microbiota-Brain Communication



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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Interventions, examples

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

103

Fasting pathways: Sirt, mTOR pathways

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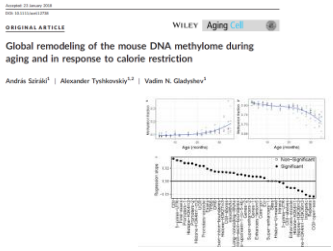
Caloric restriction and aging change epigenetic CpG -methylation structure



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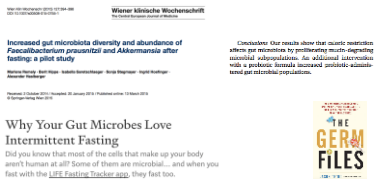
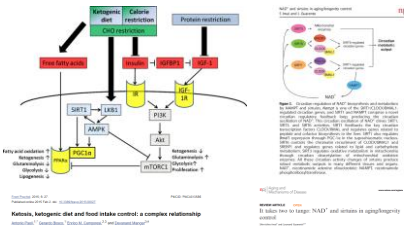
Fasting and Microbiota



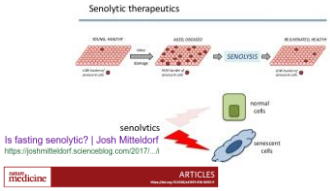
106

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



107

Caloric restriction: Rejuvenetion by senolysis? role for autophagy ?



83rd ICREA Colloquium, 2018

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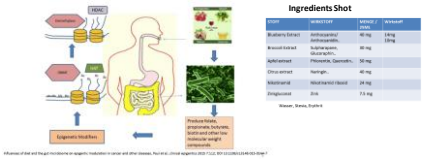
Effect of Plant Ingredient and Diet on Microbiota and Metabolites



Ingredients Shot

Shot	Wirkstoff	Menge / Shot	Verkauf
Blueberry Extract	Anthocyanins/ Anthocyanidins	40 mg	14mg 19mg
Broccoli Extract	Sulphoraphen, Glucoraphin...	80 mg	
Apfelextract	Phloretin, Quercetin...	50 mg	
Citrus extract	Naringin...	40 mg	
Mushroom'd	Reishi/Hericium	24 mg	
Ringbuster	Zink	7.5 mg	

Wieser, Stevia, Erythrit

Probiotic

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

Antimicrobial substances

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

Species

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

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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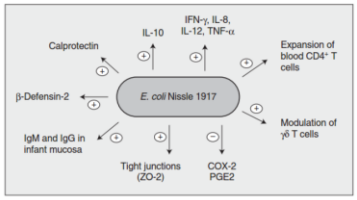

Figure 2. Various ways of immune modulation by E. coli Nissle 1917 (summary of data from in vitro and in vivo experiments) [Behnsen et al., 2013]

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Treatment of acute diarrhea with probiotics – meta-analyses

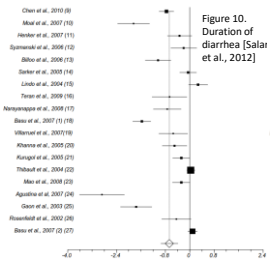

Figure 10. Duration of diarrhea [Salar et al., 2012]

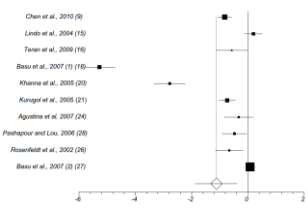

Figure 11. Duration of hospitalization [Salari et al., 2012]

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Probiotics effect the Epigenetic regulation

Article

Epigenetic aspects of new probiotic concept – a pilot study

Nina Obuća [1], Verena Schuh [1], Ulrike Krammer [1], Snezana Polovina [2], Mirjana Sumarac-Dumanovic [3], Neda Milinkovic [3], Ksenija Velickovic [4], Brizita Djordjevic [5], Alexander Haslberger [6], Nevena Dj. Ivanovic [3]*

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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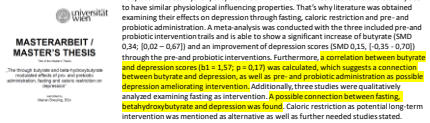
Pro-, prebiotika und SCFAS



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.

2024 AG Haslberger 118

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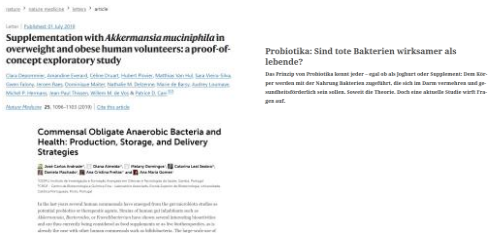
Probiotics, new ways



nature › nature medicine › letters › article

Letter | Published: 01 July 2019

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

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

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

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

José Carlos Andrade, Diana Almeida, Hilary Domingos, Catarina Leal Seabra, Daniela Machado, Ana Cristina Freitas, Ana Maria Gomes

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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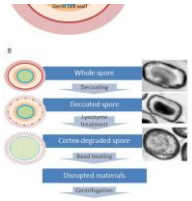
Spores



The ingredient

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

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

KENSHŌ

Natto-Sporen

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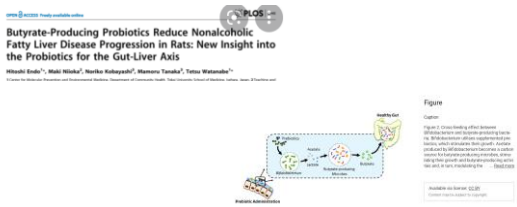
Butyrate production or cross feeding ?


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

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

Figure

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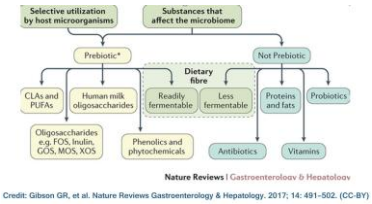
Prebiotics what is it?



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

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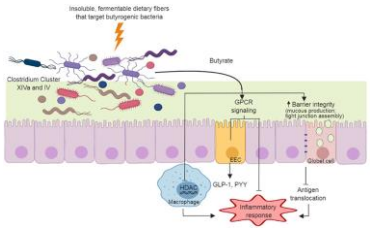
Fibers and SCFA



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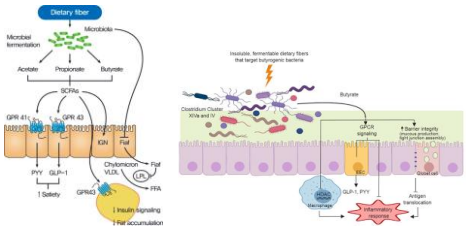
Fibers and obesity, butyrogenic



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Receptors of SCFAs

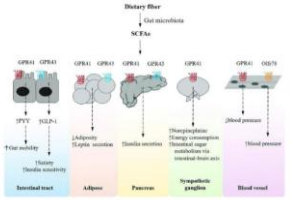

Figure 17. Short-chain fatty acid (SCFA)-receptor-mediated pathways and their effects on host energy metabolism in peripheral tissues. Gut microbes can ferment dietary fiber into SCFAs, which induce an array of G-protein coupled receptor-mediated signaling pathways that are essentially implicated in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

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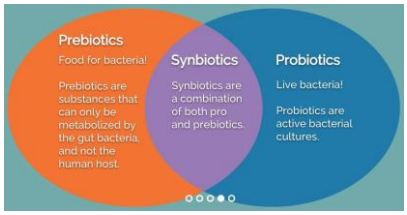
Synbiotics



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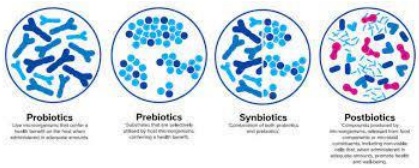

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Postbiotics

- **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

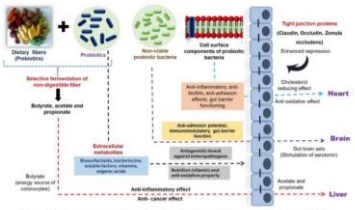

Figure 18. Schematic representation of various health benefits of postbiotic molecules [165]

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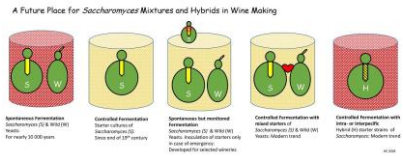
Fermentation spontaneous stater cultures



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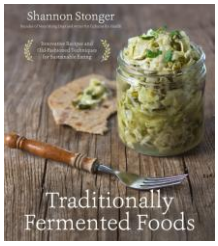
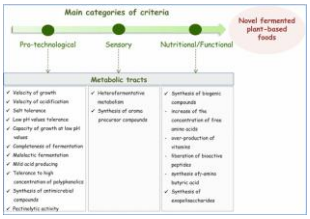
Fermentation between tradition and novel possibilities





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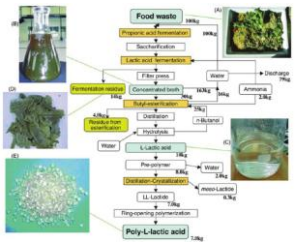
Fermentation of food waste results in usefull molecules



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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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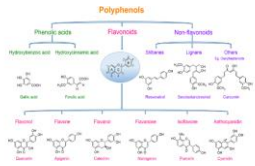
Polyphenols



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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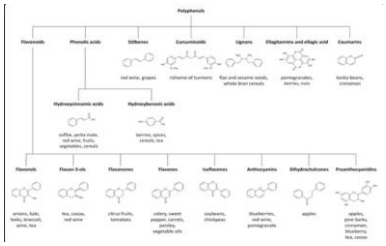
Polyphenols and their plant sources,



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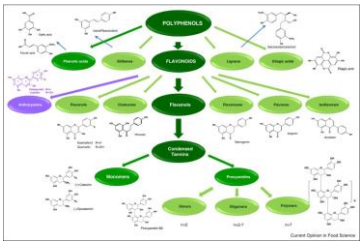
Anthocyans



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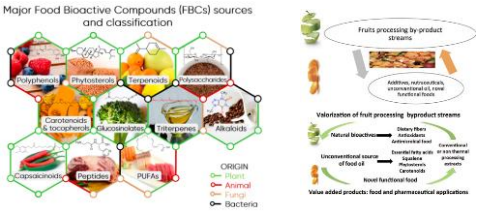
Types and classification of bioactive compounds from food



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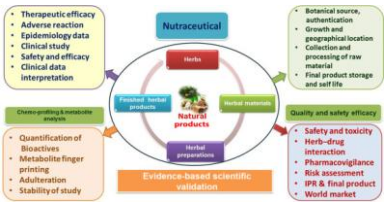
Nutraceuticals



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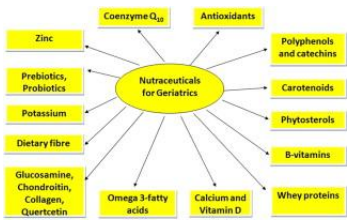
Nutraceuticals for aging



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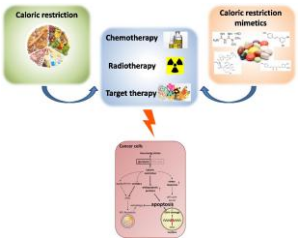
The best nutraceutical for healthy aging:CR fasting, taken as an example for desired activities



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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.

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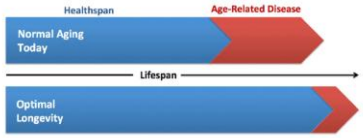
So, can we increase health span by fasting, CR ?



So what contributes to age related diseases/premature aging

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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.

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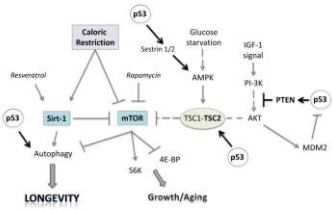
Fasting mechanisms: AMPK, SIRT, mTOR, p53



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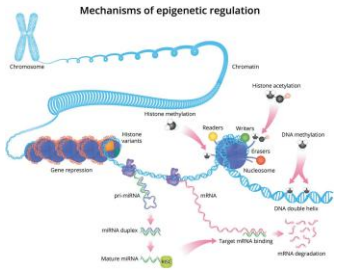

- The "above genetic"
- Impacts transcription without changing the sequence of the DNA
- originally developed as a host defense and protection of the genome stability
- silencing or activate gene expression
- Can be influenced
- Alterations have been associated with different pathologies

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

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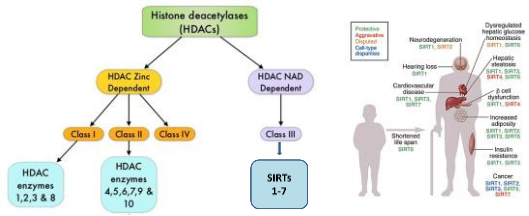
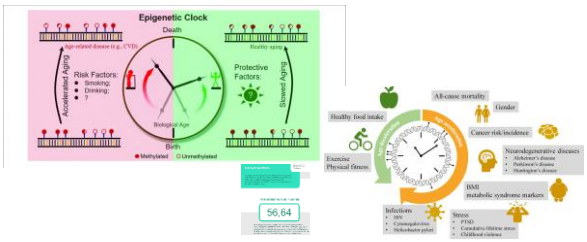
Histone deacetylases, Sirtuins



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.

146

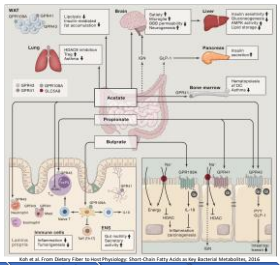
Epigenetic clock



147

The gut microbiome and SCFAs

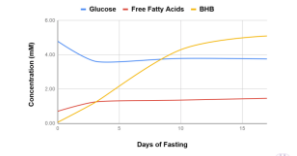
- not defined as a hallmark of aging, causal relationships have been observed between the microbiome and age
- *Firmicutes, Bacteroidetes and Actinobacteria*
- Inter-individual changes are determined by genetic, age, diet, health and geographic origin
- Composition and diversity declining with age
-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

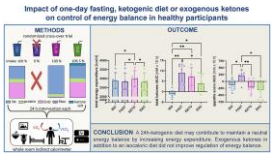


Koh et al. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites, 2016

148

CR, Fasting, Intervallfasten 18/6, ketogenesis





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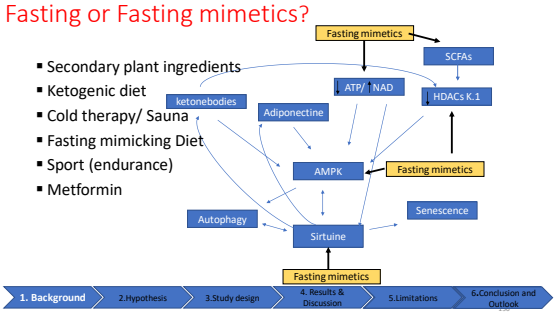
Fasting or Fasting mimetics?

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



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Aging, longevity , big business, science

151

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

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

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

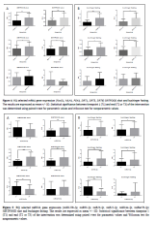
Active (N. 131) Placebo (n: 30)
Intervention 3 months

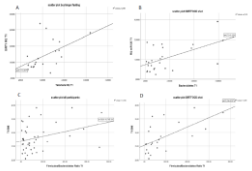
Feces, Blood spots before, after 1,3 month

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

152

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





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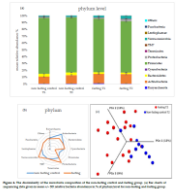
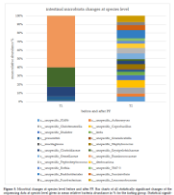
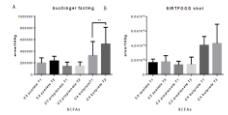
Buchinger fasting resulted in a rise in the distribution of Proteobacteria, increased microbiota diversity and a significant increase in Christensenella

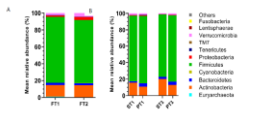




154

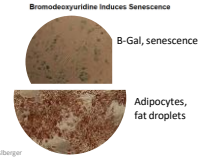
3M sirt inducing drink increased *Actinobacteria*.
Firmicutes/*Bacteroidetes* ratio decreased and correlated with BMI. Only Fasting increased Butyrate significantly





155

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



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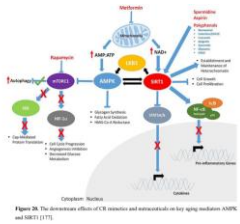
CR, fasting mimetics,



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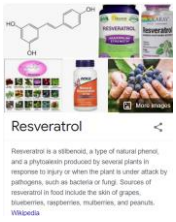
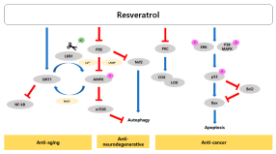
Examples,
Resveratrol





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

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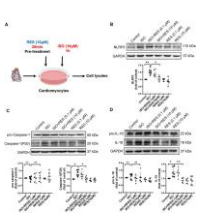
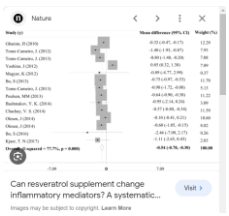
Resveratrol Vitro : Vivo





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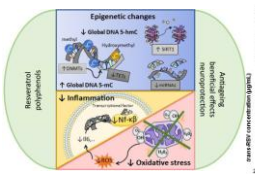
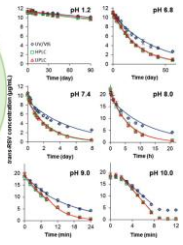
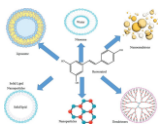


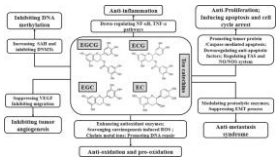




Novel food ?!

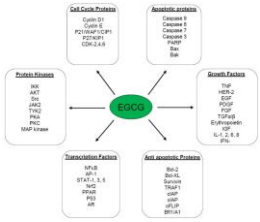
160

Green tea extract, EGCG, Catechines



161

EGCG

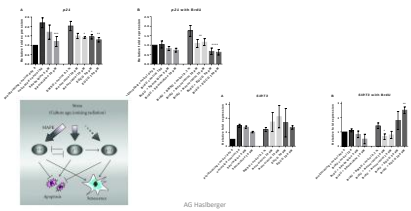


162

EGCG II

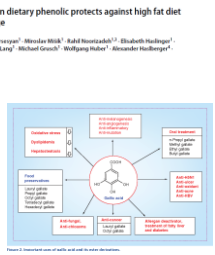
163

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



164

Gallic acid



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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

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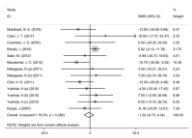
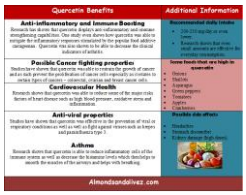


167

Quercetin



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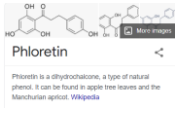
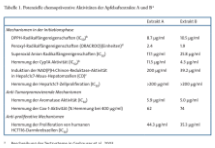
Phloretin





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

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Food & Function

ROYAL SOCIETY OF CHEMISTRY

PAPER

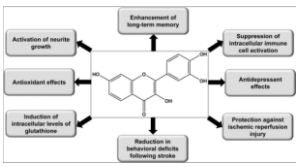
Assessment of human inter-individual variability of phloretin metabolites in urine after apple consumption. AppleCOR study†

: 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.

170

Fisetin



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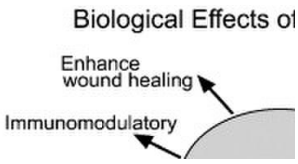
Curcumin



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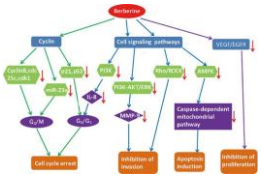
Berberin, Berberitze



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Anthocyans

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Spermidin

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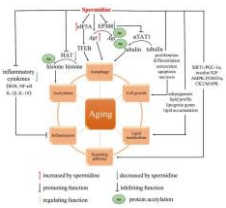
Spermidin mechanisms



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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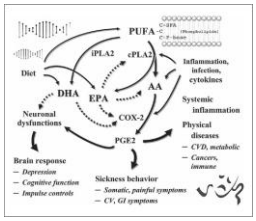
Fishoil, EPA, DHA



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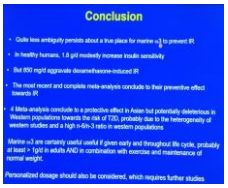
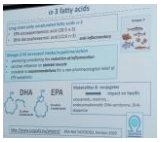
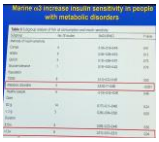
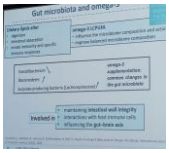
Fishoil II









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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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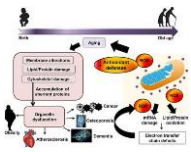
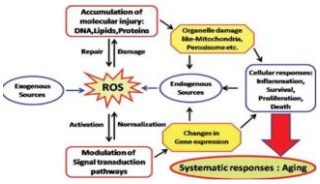
ROS and antioxydative activities





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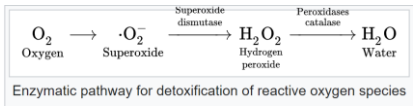
Antioxydants

Antioxidant	Solubility	Concentration in human serum (μM)	Concentration in liver tissue (μmol/kg)
Ascorbic acid (vitamin C)	Water	50–60[272]	260 (human)[74]
Glutathione	Water	4[273]	6,400 (human)[74]
Lipoic acid	Water	0.1–0.7[274]	4–5 (rat)[57]
Uric acid	Water	200–400[275]	1,600 (human)[74]
Carotenes	Lipid	β-carotene: 0.5–1[276] retinol (vitamin A): 1–3[277]	5 (human, total carotenoids)[51]
α-Tocopherol (vitamin E)	Lipid	10–40[278]	50 (human)[74]
Ubiquinol (coenzyme Q)	Lipid	5[132]	200 (human)[132]



Enzymatic pathway for detoxification of reactive oxygen species

181

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

Promotor CpG methylation

Histones

DNA - packaging

Non-coding miRNAs

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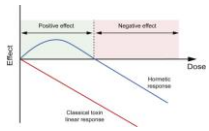
Stress and Mitormesis



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.

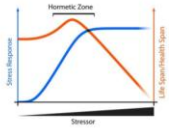

Figure 11. Mithormesis Theoretical curve showing how low doses of a stressor may have beneficial effects by activating intracellular stress response pathways. If the stressor exceeds the capacity of the stress response system to maintain homeostasis, then deleterious phenotypes are observed.

184

Novel foods, functional foods and epigenetics

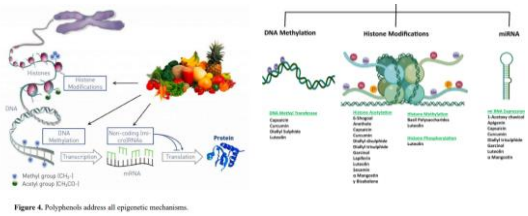

Figure 4. Polyphenols address all epigenetic mechanisms.

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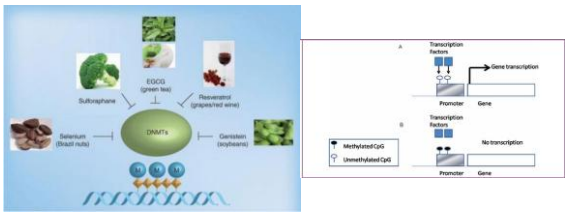
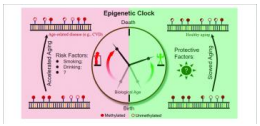
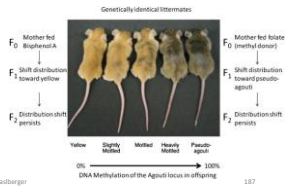
DNA, CpG methylation



186

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

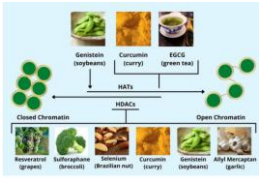
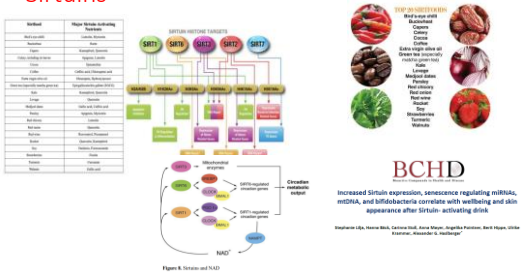


Figure 6. Effects of epigenetic active plant ingredients on histones, chromatin, and gene expression

188

Sirtuins



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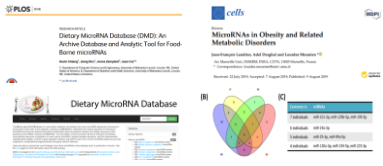
Epigenetic miRNAs: food borne, marker for mechanisms, phenotypes, disorders



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Mi RNAS, non coding RNAs

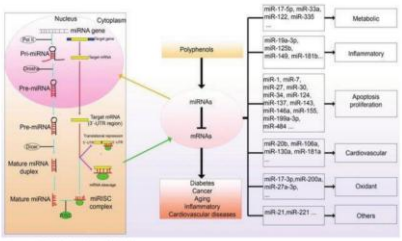

Figure 9. Polyphenols and ncRNAs

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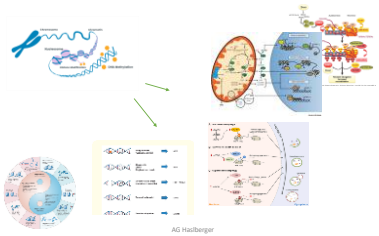
Epigenetics regulates aging mechanisms involved in telomere attrition, mitochondrial functions, autophagy, I.S./inflammation, senescence and DNA-repair



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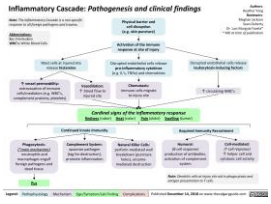
Polyphenols and Inflammation mechanisms



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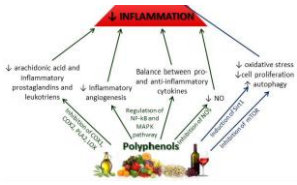
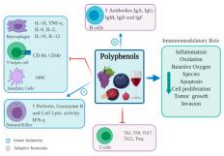
Polyphenol effects inflammation:





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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.

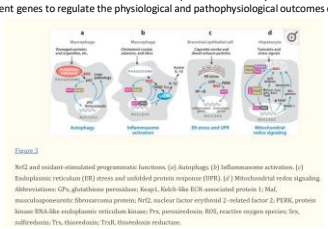

Figure 3

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

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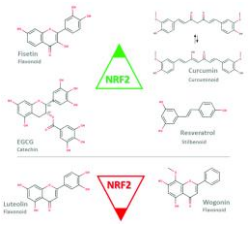
NRF2 agonists, antiagonists



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Neuro- inflammation

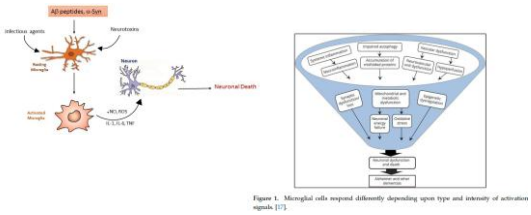

Figure 1. Microglial cells respond differently depending upon type and intensity of activation signals. [17].

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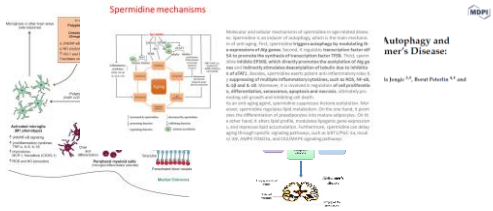
Polyphenols, spermidin and microglia



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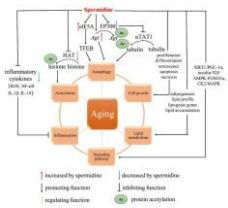
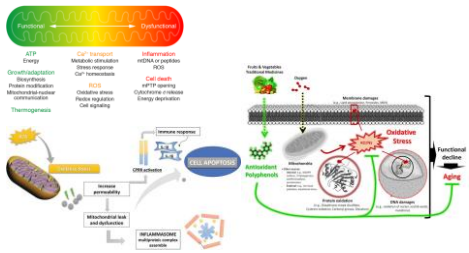
Spermidine mechanisms



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 **indirectly stimulates deacetylation of tubulin due to inhibition of aTAT1.** Besides, spermidine exerts potent anti-inflammatory roles by **suppressing of multiple inflammatory cytokines, such as ROS, NF-κB, IL-1β and IL-18** . Moreover, it is involved in regulation **of cell proliferation, differentiation, senescence, apoptosis and necrosis**, ultimately promoting cell growth and inhibiting cell death.
As an anti-aging agent, spermidine suppresses histone acetylation. Moreover, spermidine regulates lipid metabolism. On the one hand, it promotes the differentiation of preadipocytes into mature adipocytes. On the other hand, it alters lipid profile, modulates lipogenic gene expressions, and represses lipid accumulation. Furthermore, spermidine can delay aging through specific signaling pathways, such as SIRT1/PGC-1α, insulin/ IGF, AMPK-FOXO3a, and CK2/MAPK signaling pathways.

199

Polyphenols and mitochondria, the oldest theory of aging



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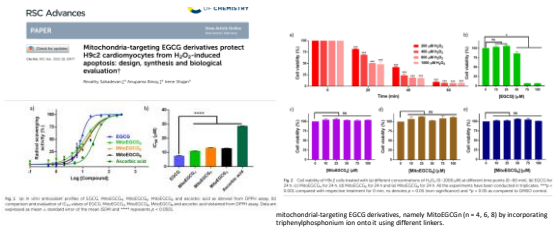
Mitochondria directed EGCG protects from H2O2 induced cell apoptosis



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

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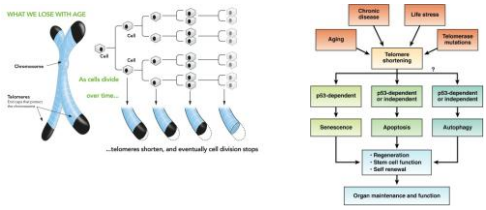
Telomer attrition



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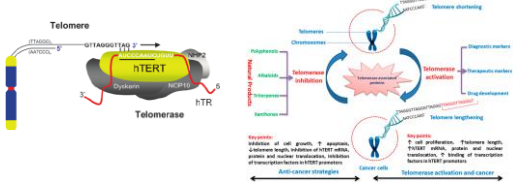
Telomers, telomerase



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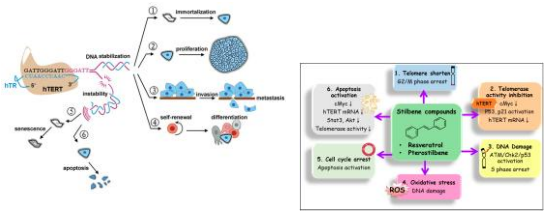
Polyphenols in the regulation of telomerase, hTERT



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Anti-aging agents	Sources	Positive efficacy	Ref.
Cycloastragenol (TA-65)	Astragalus membranaceus	Telomeraseactivator	[5, 41]
GRN510	GRN685/TAT2	Telomerase activator	[88]
AGS-500	Synthetic triaryl compounds	Telomerase activator	[36]
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, 39]
Ginsenosides	Natural triterpene saponins	SIRT1 activator	[33]
Melatonin	Hormon	SIRT1 activator	[14]
Navitoclax	Synthetic compound	Senolytics via Bcl2/Bcl-xL	[23]
Dasatinib+Quercetin	Synthetic compound+ Natural flavonol	Senolytics via p53/p21, tyrosinase kinase	[36]
Fisetin	Natural polyphenol	Senolytics via PDK/Akt	[40]
17-DMAG	Synthetic compound	Senolytics via HSP90	[14]
Gal-fisocamycin	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

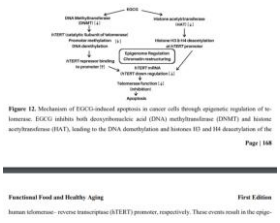

Figure 12. Mechanism of EGCG-induced apoptosis in cancer cells through epigenetic regulation of telomerase. EGCG inhibits both deoxyribonucleic acid (DNA) methyltransferase (DNMT) and histone acetyltransferase (HAT), leading to the DNA demethylation and histones H3 and H4 deacetylation of the

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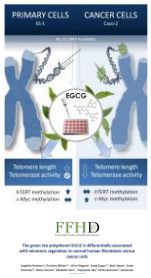
human telomerase- reverse transcriptase (hTERT) promoter, respectively. These events result in the epige-



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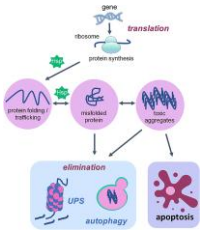
Autophagy, apoptosis



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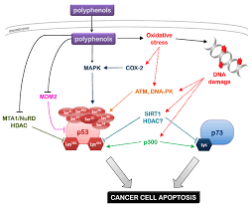
Apoptosis, p53 and polyphenols



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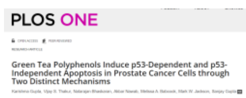

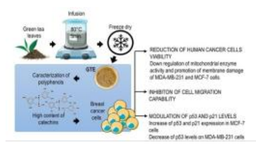

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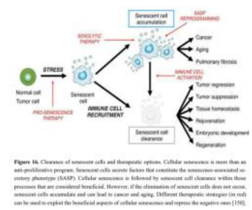
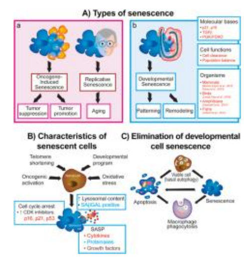
Senescence and polyphenols





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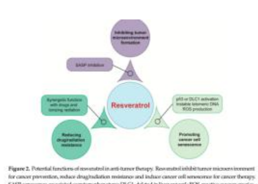
Polyphenols and senescence



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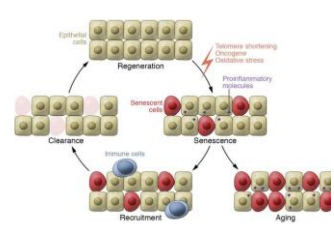
Senolytics between rejuvention of tissues and cancer prevention



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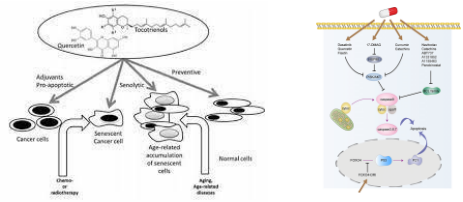
Quecetin, senolytics and markets millio $ markets



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Immuno senescence and nutraceuticals

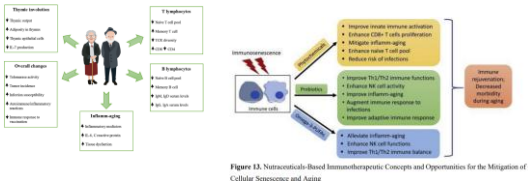

Figure 13. Nutraceuticals-Based Immunotherapeutic Concepts and Opportunities for the Mitigation of Cellular Senescence and Aging

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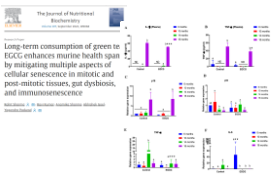

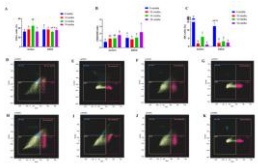

Effect of EGCG consumption on innate immune functions. Animals were divided into four control groups and four EGCG fed groups, and one group each from control and EGCG groups was sacrificed after every 4 months of feeding till 18 months of animal age. Plasma levels of (A) IL-1β (B) TNF-α.

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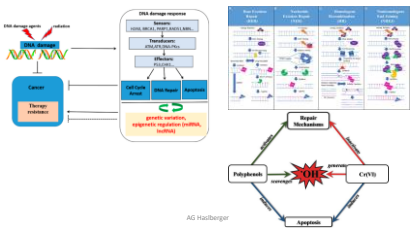
Aging DNA-damage response, DNA-repair, Epigenetics, Polyphenols



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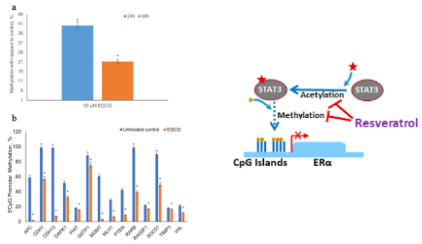
MGMT and MLH1 DNA repair enymes and promotor methylation, EGCG



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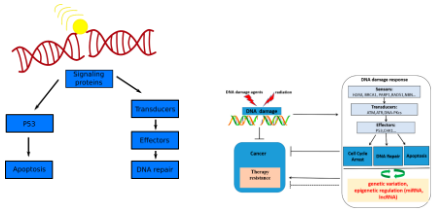
Epigenetics regulates DNA repair



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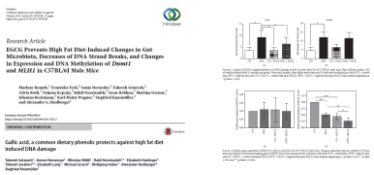
Mouse study: EGCG reduced high fat diet induced strandbreaks, DNmt1, comet assay



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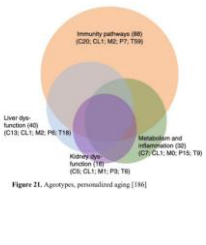
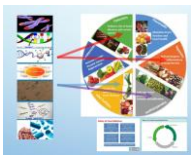
Aging, ageotypes and prevention





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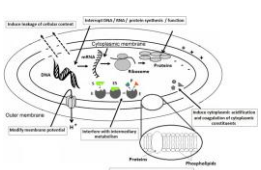
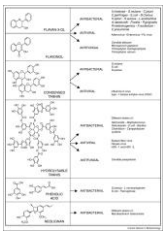
Anti bacterial polyphenols





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Antiviral nutraceuticals

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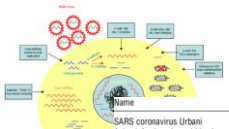
RNA and Corona viruses



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 • HIVluc/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 0.153 mM. LD_{50} in mice was 232.2 mg/kg	Yi et al. 2004[17]
2	Quercetin	SARS-CoV S2 protein	HIVluc/SARS pseudotype virus assay	EC_{50} of 83.4 μM and CC_{50} of 337 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 100 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	• 88% inhibition at 100 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 100 μM. • IC_{50} of 73 μM • Binding energy −11.7 kcal/mol	Nguyen et al. 2012[18]
6	Resveratrol	MERS-CoV NP	• MTT assay using vero-E6 cell line • Nucleocapsid protein staining	• Found to be effective in the 125–250 μM range on viral titre as well as viral RNA amount. • Inhibits caspase 3 cleavage.	Lin et al. 2017[19]
7	Hesperetin	SARS-CoV 3CLPro	Cell free and cell-based cleavage assays	IC_{50} of 68 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 AURN	• Gene silencing • Expression studies • Transgenic mouse models	• Quercetin affected ACE2 expression. • In addition, it was found to alter the expression of 98 of 332 (30%) genes encoding human proteins that serve as target for the SARS-CoV-2.	Glinsky, 2020[21]

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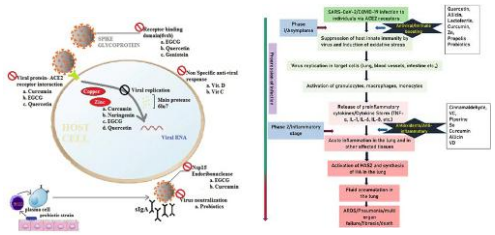
Covid , SARS-2



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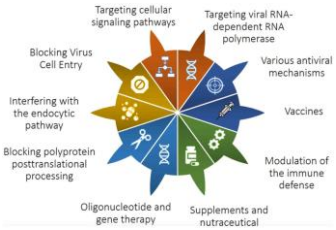
Strategies



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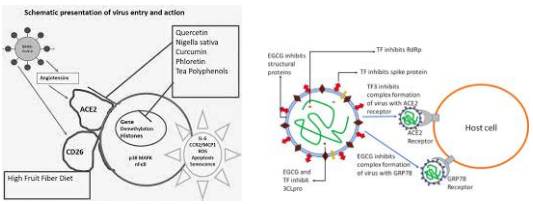
Nutraceuticals, epigenetics and inhibition of RNA viruses



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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

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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.

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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.

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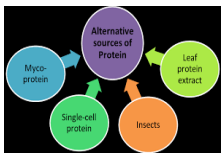
Novel Protein Sources



Protein-energy malnutrition is a global challenge that demands urgent attention, especially with the increasing population growth and unmatched food security plans. One strategy is to expand the list of protein sources, such as neglected and underutilized crops, with high protein content. A good number of plant proteins, in addition to their nutritional benefits, exert therapeutic properties

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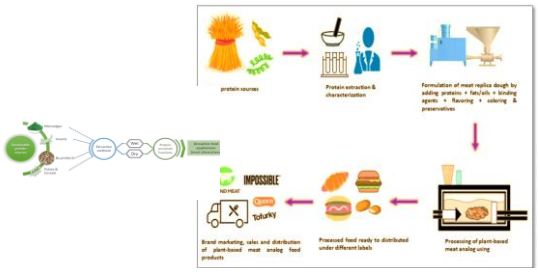
Novel protein sources, meat replica



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Proteins from microorganisms , single-cell proteins (SCPs)

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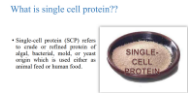
Single cell proteins



- 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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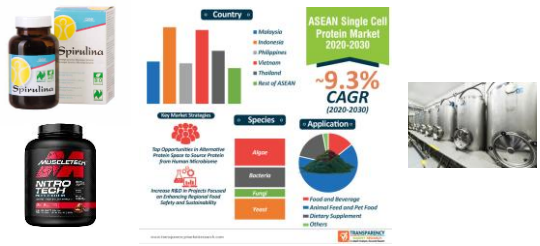
A mega market



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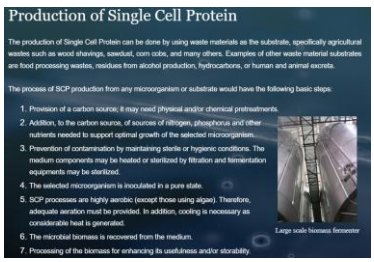
Single cell proteins , fermentation, (often) using waste materials)



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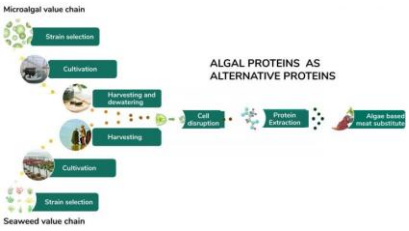
Protein (and other goodies) from algae



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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

Potential and legal framework

Tomke F. Prüser, Peggy C. Braun, Claudia Wlacek

Abstract

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

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

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

Microalgae

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

The algae group is divided into microalgae and macroalgae, whereby macroalgae are multi-

Microalgae in the food industry

Microalgae such as Chlorella and spirulina have considerable dietary potential due to their spectrum of nutrients. They thus became a focus of research as early as 1950 and the first microalgae were cultivated and marketed on a commercial scale from 1960 [8]. Since then interest in microalgae has steadily increased due to their adaptability and the number of different constituents which can be obtained from them [8, 11]. Whereas initially microalgae were sold mainly as nutritional supplements in the form of powders, capsules, and tablets, today they are also incorporated into various products like pasta, smoothies, soft drinks, chocolate, and ice cream [12, 13]. In 2018 the global market volume for microalgae products was already USD 9.8 billion and with a projected annual growth rate of over 7% market volume could reach USD 14.99 billion by 2024 [14]. There are large production plants in countries such as Israel, United States, Australia and China. In Germany too there are at least 13 plants producing microalgae [15].

Molke

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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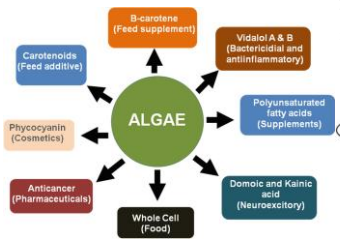
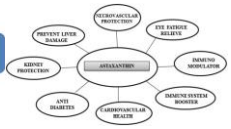
Goodies from algae



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



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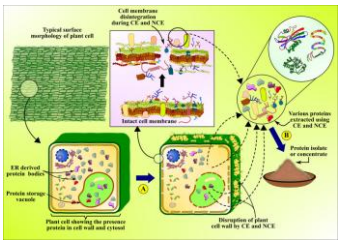
Plant protein sources, non-conventional extraction techniques (NCE)



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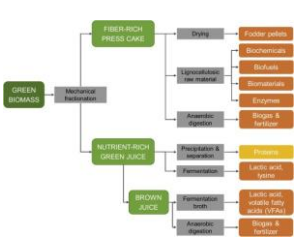
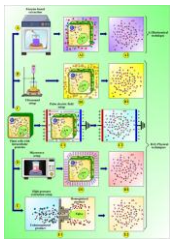
Plant protein sources, methods





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Plant-based proteins

- 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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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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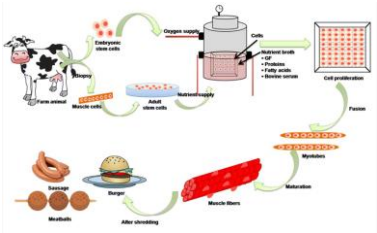
Cultured meat, production



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 butyricum		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/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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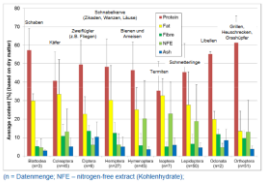
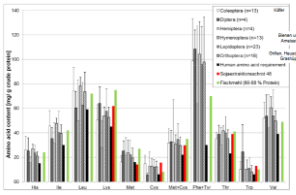
Durchschnittliche Zusammensetzung verzehrter Insekten



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

Aminosäurespektren verzehrter Insekten



[BfR, 2016]

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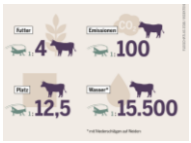
ökologische und ökonomische Vorteile

- 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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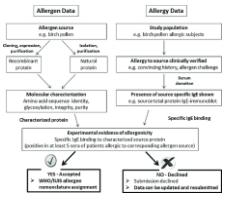
Main problem allergy in all novel protein sources



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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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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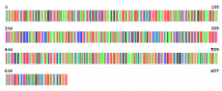
Nachweismethode Insekten

- 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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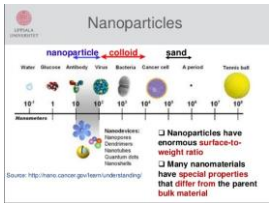
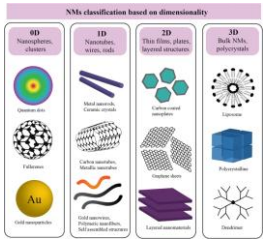
NANO particles, nutrition and foods





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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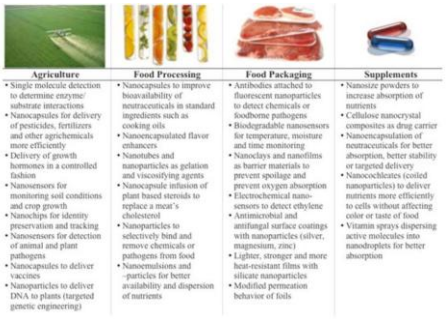

Agriculture	Food Processing	Food Packaging	Supplements
• Single molecule detection to determine enzyme/ substrate interactions • Nanocapsules for delivery of pesticides, fertilizers and other agrichemicals more efficiently • Delivery of growth hormones in a controlled fashion • Nanosensors for monitoring 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 • Nanocochleates (coiled nanoparticles) to deliver nutrients more efficiently to cells without affecting color or taste of food • Vitamin sprays dispersing active molecules into nanodroplets for better absorption

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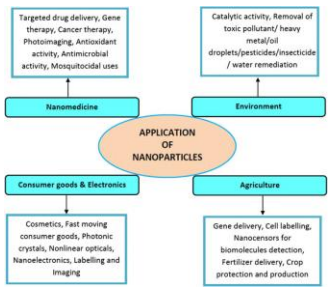

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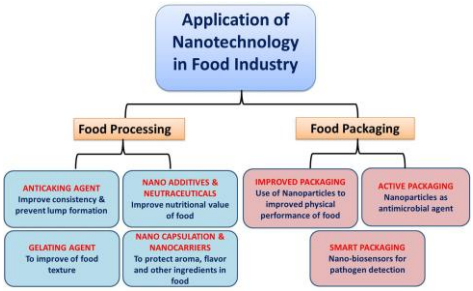

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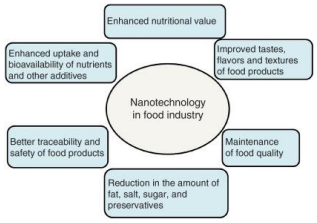
Nano and nutrition



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Methods Nano

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

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Nanoparticles: Delivery, stability, release

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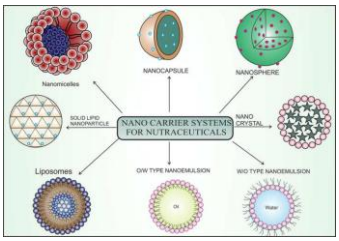
Nano carriers



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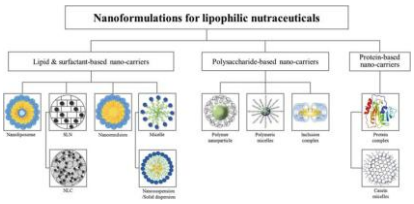
Nano and nutraceuticals



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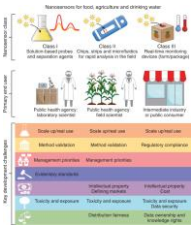
Nano sensors



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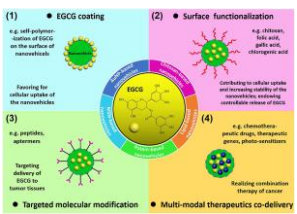
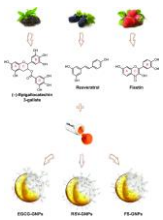
Nutraceuticals delivery





Gold nanoparticles , GNPs

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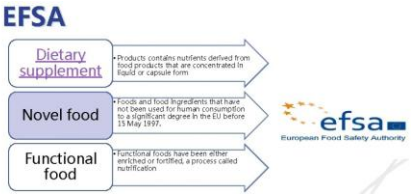
Supplements, NF, functional foods



Nutraceuticals, Botanicals
Foods for special medical purposes

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Supplements,Food improvements

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Safe level

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

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

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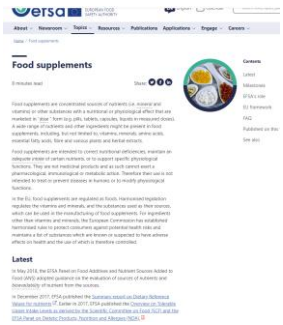
Supplements , EU upper intake levels



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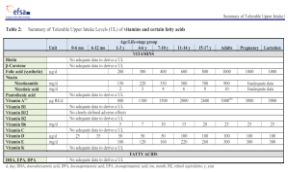
Supplements Intake levels



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Botanicals EU

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Foods for special medical purposes

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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 occurring 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

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Example, botanical

COMPENDIUM OF BOTANICALS REPORTED TO CONTAIN NATURALLY OCCURRING 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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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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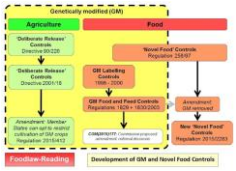
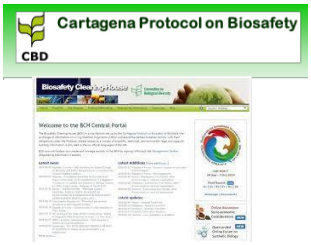
Developments novel food regulation, vertical, horizontal





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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

VESIsorb® Drug Delivery System

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

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

Questions of interpretation on the Novel Food Regulation - Topic Spermidine

26. June 2022 — by Jakob Hüttmair-Brandauer in Life Sciences

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

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

The court referred the following questions to the ECJ:

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

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

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

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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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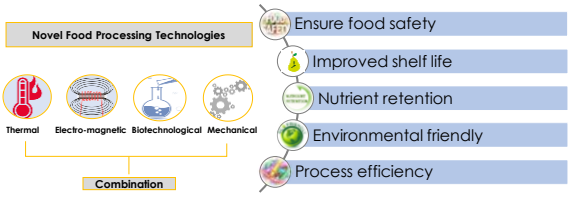
Novel foods because of processing technologies



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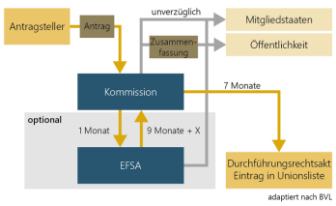
Authorisation process



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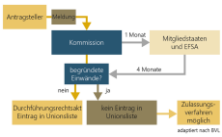
Notification of a traditional food from third countries

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 countries can be viewed online at the European Commission.



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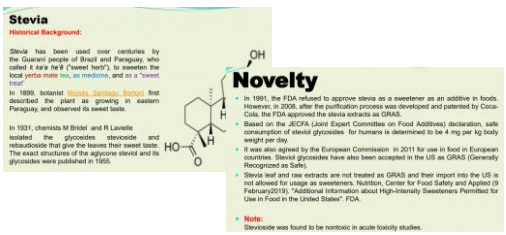
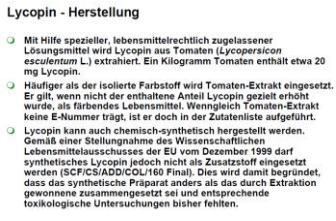
Examples, Stevia



299

Lycopin



300

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 6. September 2006 erneut die Sicherheit von Noni-Saft bewertet. Sie war von der Europäischen Kommission um eine wissenschaftliche Stellungnahme gebeten worden. Sie sollte bewerten, ob die berichteten Fälle von akuter Hepatitis einen Einfluss auf die Sicherheit von Noni-Saft haben würden.
- Noni-Saft ist seit 2003 als neuartiges Lebensmittel zugelassen, vermarktet zu werden. Das NDA-Gremium der EFSA kam zu dem Ergebnis, dass es keine wirklichen 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

2.7 Baobab-Fruchtfleisch

Taxonomie, traditionelle Verwendung

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



Sicherheitsbewertung

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

The following facts should be taken into consideration:

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

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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 (Teriaka Ltd)
- milk type products and yoghurt type products with added phytosterol esters
- yellow fat spreads, milk type products, yoghurt type products, and spicy sauces with added phytosterols/phytostanols (Pharmaconsult Oy Ltd. (formerly MultiBene Health Oy Ltd))
- yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks and cheese type products with added phytosterols/phytostanols

2000-2003
- Salatrim
- oil rich in DHA
- 'noni juice'
- coagulated potato proteins and hydrolysates thereof
- dextran preparation produced by Leuconostoc mesenteroides.
- pasteurised fruit-based preparations produced using high-pressure pasteurisation.
- trehalose
- "yellow fat spreads with added phytocolesterol esters"
- "phospholipides from egg yolk"

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

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

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

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

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

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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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Nutrition, disease prevention Functional foods, additives health claim regulation

- Lebensmittel vs. Arzneimittel?
  - Bei Pflanzen-Extrakten große kulturelle Unterschiede in den Mitgliedstaaten der EU
    Länder mit langer Tradition, aber sehr unterschiedlichen Handhabungen (pos. vs neg. Liste, LM vs. AZM)
- Neuartig (Novel Food) oder nicht?
  - Vielfältige und nicht konsistente Interpretation sowohl auf Mitgliedstaaten als auch EU-Ebene
  - **Folge** → große Unsicherheiten, eingeschränkte Entwicklungsmöglichkeiten

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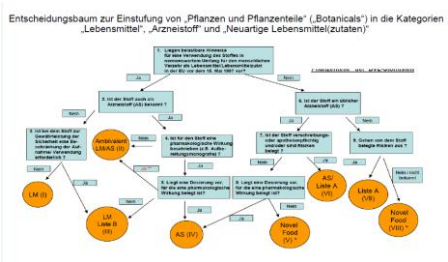
Food or medicine ?



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Kennzeichnung claims Regional differences

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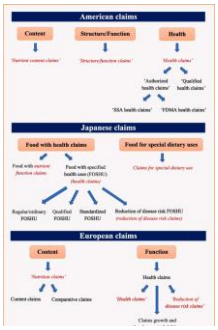
Regional differences



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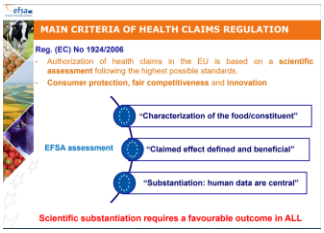
Health claim regulation



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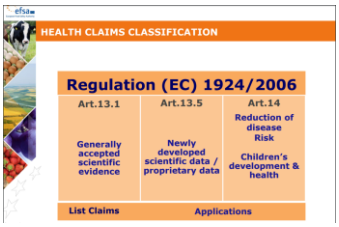
Health claim classification



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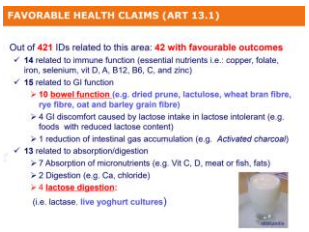
Examples 13.1



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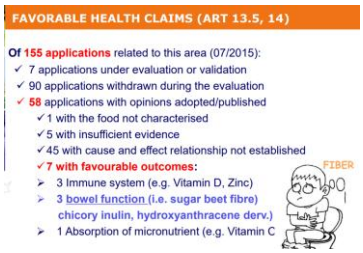
Examples 13.5



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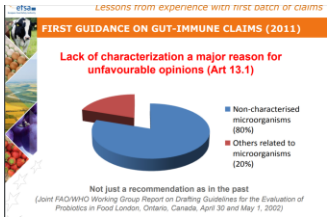
Problems of gut immune claims (eg probiotoics



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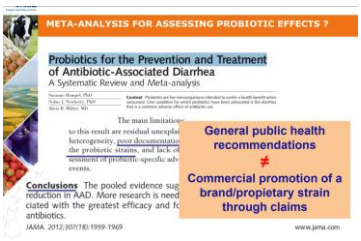

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New developmements

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Spermidine

Scientific output

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

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

Published: 30 June 2011

Scientific output

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

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

Published: 7 December 2011

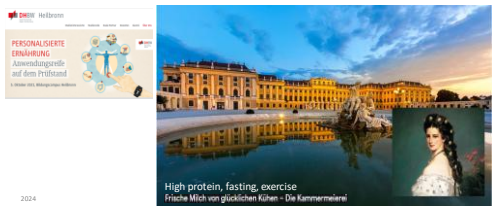
Scientific output

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

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

321

Personalisation and novel foods



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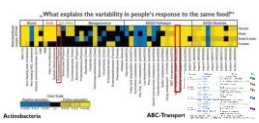
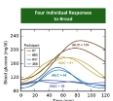
Highly different personal responses to diets, eg post- prandial glycemic responses, explanations ?





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

2024 AG Hadlberger 323

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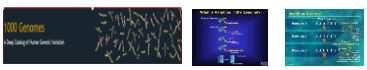
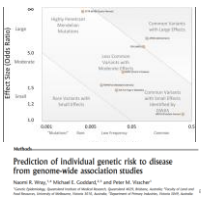
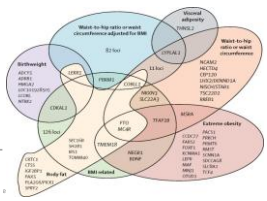
GWAS : SNPs, common variants have often only moderate effects; in different metabolic areas







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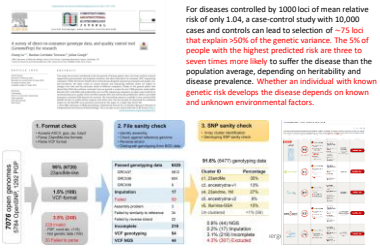
despite low penetrance of SNPs, D-T-C genetic testing for nutritional advice



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

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

Melanocortin

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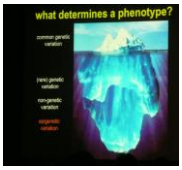
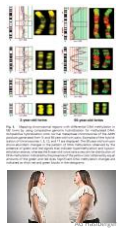
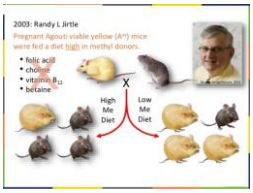
Missing heritability: what is missing to understand a phenotype: gene- environment interactions, epigenetics, reversibility







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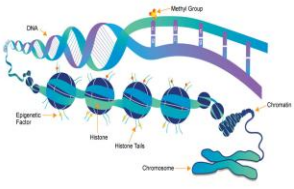
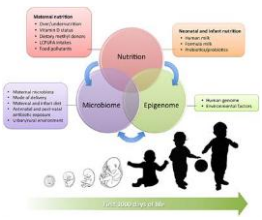
Epigenetics mechanisms, Interactions, early imprinting





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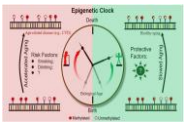
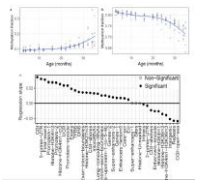
CpG Methylation, Epigenetic clock, reflect C.R., nutrition

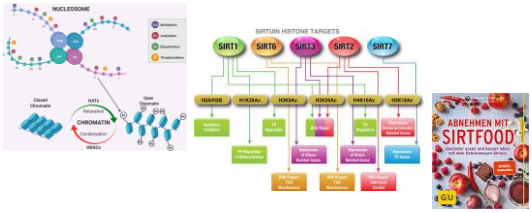


Intrinsic age: Horvath multiple tissues.
Extrinsic Hannum, blood cell



328

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



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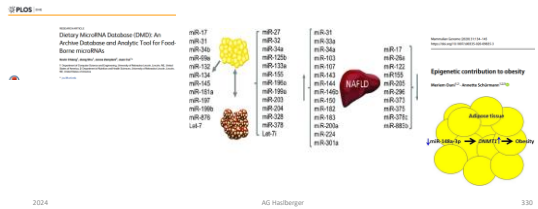
Epigenetic miRNAs: food borne and regulators and markers of metabolic mechanisms, phenotypes, disorders



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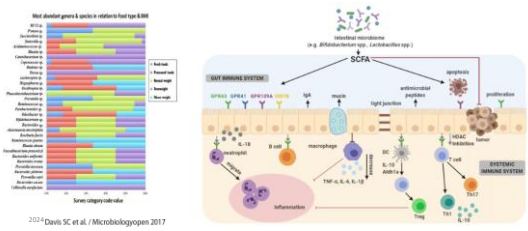
High Individual diversity of gut microbiota reflects nutrition and lifestyle , results in different expression of metabolites esp. SCFAs



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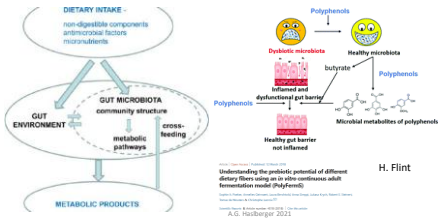
highly personal different responses of microbiota to diets, (crossfeedinG) and metabolisation of foods



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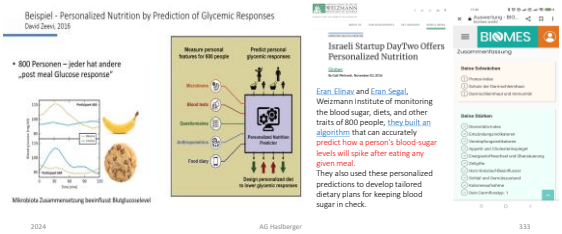
Correlation of microbiota structure with Glycemic responses used for algorithms for dietary advice



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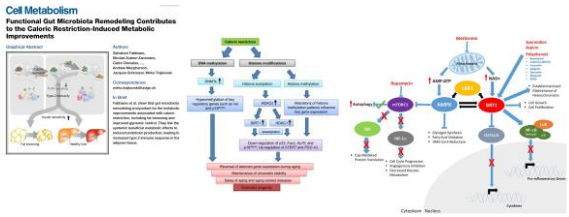
So, Genetic and microbiota analysis for personal dietary plans, But of central importance are Interactions microbiota with epigenetic System; host gut interactions e.g. in C.R., Fasting (fasting Mimetics)



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

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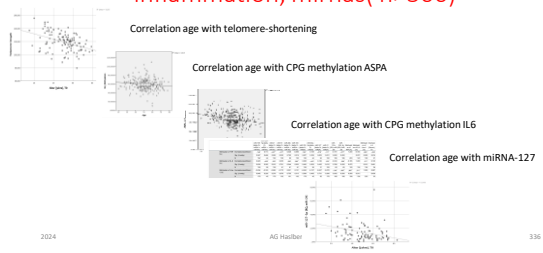
Faces of personal aging: correlations of age with telomers, CPG-methylation, inflammation, mirnas(n>500)



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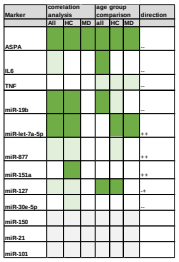
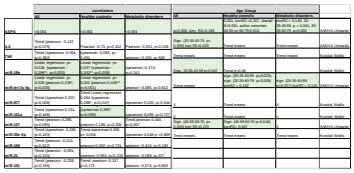
Age dependent epigenetic markers: In the Metabolic disease group (MD) correlations are disrupted, n>300





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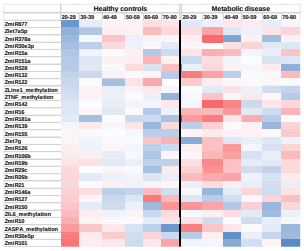
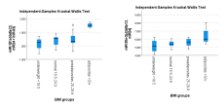
different aging patterns (age related Mirnas) in metabolic disease group



Marker	All	healthy controls	metabolic disorders
mir-181a	0.454* (Pearson)	x	0.727**
mir-378a	0.396* (Pearson), Linear regression (p=0.28)	x	0.954**
mir30e-5p	-0.339	-0.429	0.357
mir22e-3p	0.365* (spearmanr), Linear regression (p=0.0421)	x	0.573
mi122	x	-0.359	x
mi101	x	-0.353	x
let7a	x	-0.360*	x
mir39*	p=0.007	p=0.024	

*Kruskal Wallis test between BMI groups



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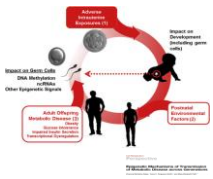
Conclusion: Complex diseases (Aging) can arise from (a mixture of) personal diverse causes, an argument in favor of personally specific interventions (e.g. metabolic disease)



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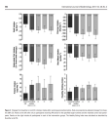
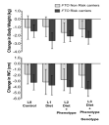
Conequences for Intervention: Flagship EU-Food4me study results prove „personal nutrition does better than on size fits all“, J. Mathers



Changes 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 nonpersonalised group

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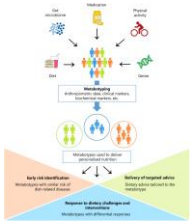
Definition of metabotypes from genetic-, microbiota-metabolomics based information, Metabotyping



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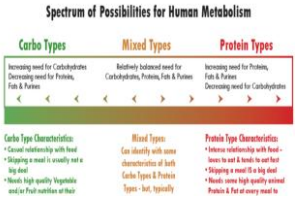
Consequences of MetAbotypes, diets nexT step trackers



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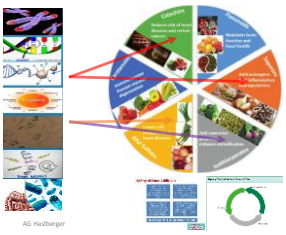
Personalisation of additives for Prevention
Monitoring basic hallmarks of health/aging. Use of mixes of supplements, functional foods which address specific mechanisms „Achilles Fersen Concept“



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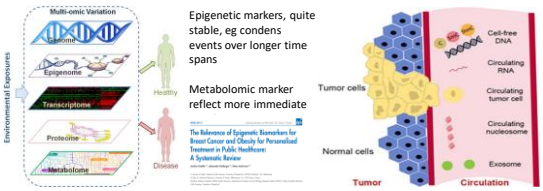
Importance of good Markers, Nutrition: following the way of personalised, prezision medicine, CFDNA) ?



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

Metabolomic marker reflect more immediate

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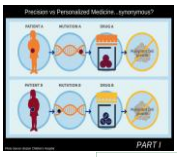
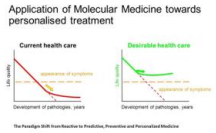
Prevention, intervention, Salutogenesis personal or precision medicine, synonyme? personal or precision nutrition, synonyme?





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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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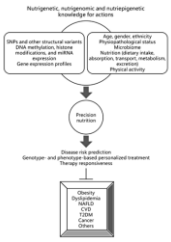
Precision-, personalised nutrition, the way we may go



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).

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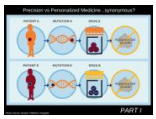
Prevention, intervention: personal precision medicine, personal precision nutrition



Objectives aging:
- longevity,?
- healthy life span ?
- age related complex diseases?

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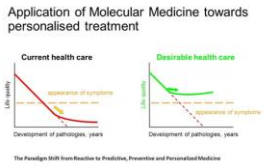
Analysis of molecular markers of different aging mechanisms and functional foods adressing the personal hazard may contribute to a personal, preventive health care, disease prevention, healthy aging



Objectives aging:
- longevity,
- healthy life span
- age related complex diseases?

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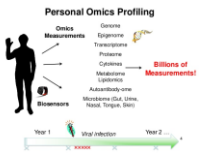
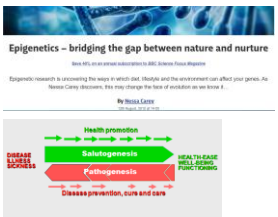
Epigenetic and Salutogenesis : the bridge between scientific reductionism of markers and mechanisms and the need address the entire person ?





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