Nutraceuticals: a new paradigm of pro active medicine.

Antonello Santini

Department of Pharmacy, University of Napoli Federico II
e-mail: asantini@unina.it

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Àha¯rasambhavam vastu roga¯s' ca¯ha¯rasambhava¯h, Hita¯hitavis' esa¯s' ca vis' esah sukhaduhkhayoh

Caraka Samhita Sutrasthana (1, 28:45)

“The physical body is the product of diet and sensory input (lifestyle). Similarly, all diseases are the result of non correct diet and lifestyle. Diet and lifestyle wholesome and unwholesome are the foundations of health and illness”

Caraka Samhita Sutrasthana (1, 28:45)

The definition of health status.

"Health is a state of complete well-being, physical, mental and social, and not merely the absence of disease"

(World Health Organization, 1947)

The main focus.

"Do not be
worried on how to add days
to our life, but on how to give
more life to our days"

(Dame Cicely Mary Saunders)

Some preliminary considerations on handling an health condition.

i. The **olistic medical approach**.
ii. The **static approach**: the patient, often unaware of a potential health risk, waits till the clear signs of the onset of a disease appear (watchful waiting or active surveillance medicine) and then obtain a diagnosis and starts using prescription drugs.
iii. The **nutraceutical dynamic approach** also known as "**initiative medicine or proactive medicine**": taking preventive action before the onset of a disease instead of waiting for the disease to become evident.

The availabile tools.

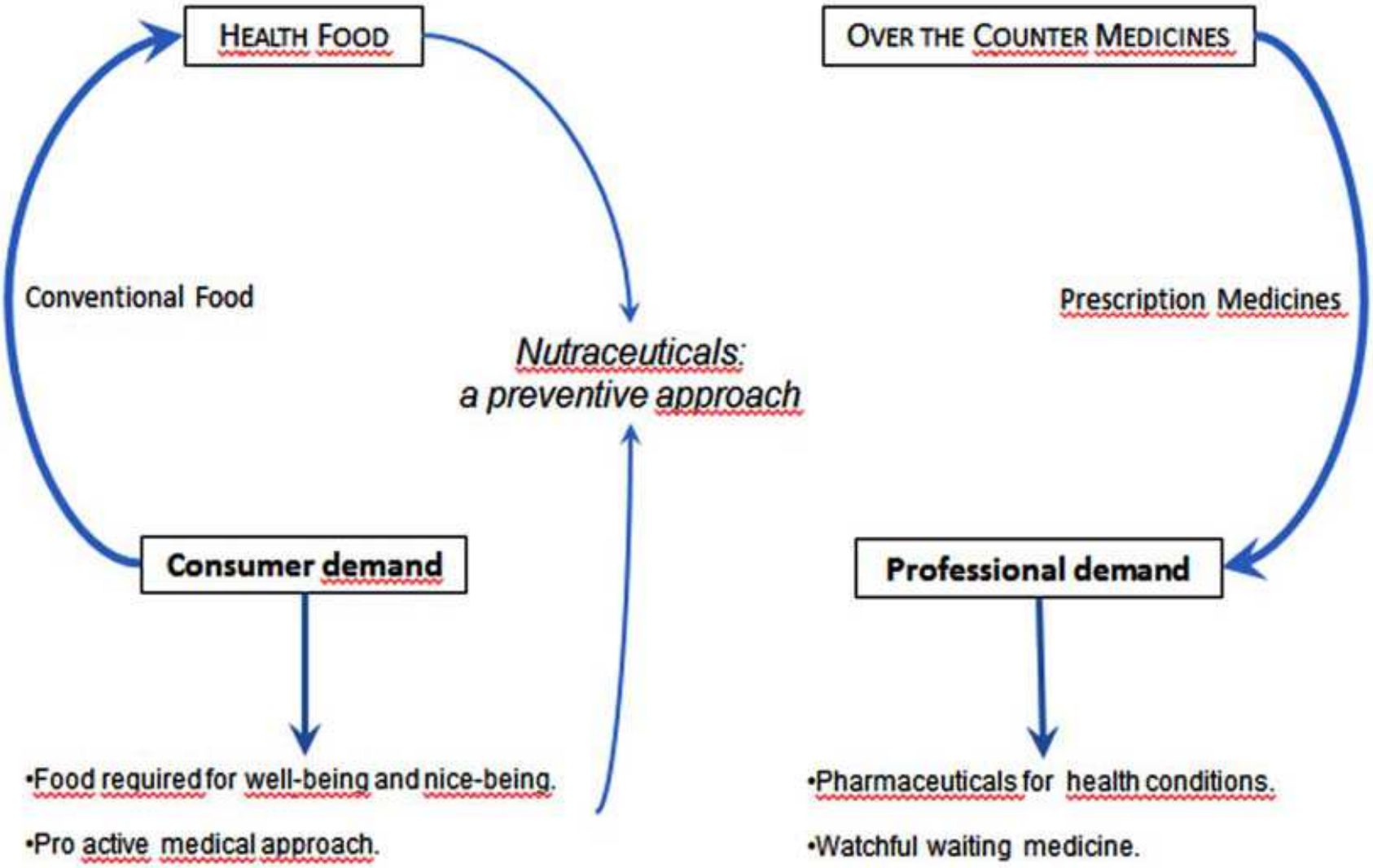
Primary prevention
Secondary prevention

- Lifestyle – behaviour – dietary habits

Possible approaches:

- Drugs (waitchful waiting medicine)
- Nutraceuticals (pro active medicine)

The possible approaches.



Nutraceuticals: TORs.

- 1989 Stephen DeFelice, President of the Foundation for Innovation in Medicine (Cranford), NJ, USA.

Nutraceutical: food or part of food that provides medical or health benefits, including the prevention and/or treatment of a disease.

(Merriam-Webster, 2013)

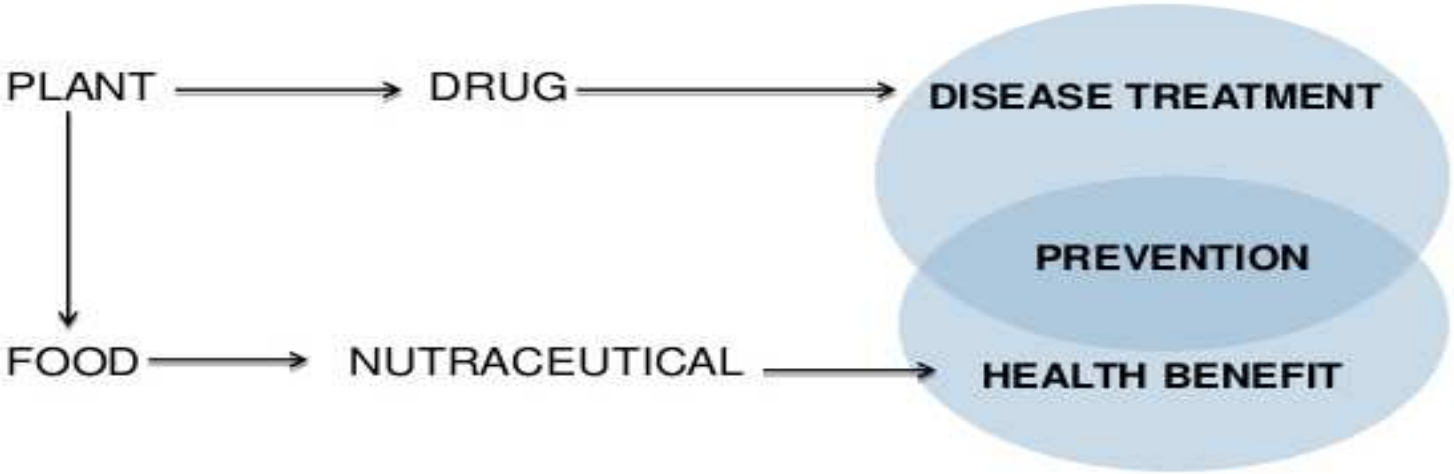
Nutraceuticals: TORs.

The term **nutraceutical** refers to products for oral use containing high concentrations of active principles derived from food, and provide health benefits from a preventive and/or therapeutic point of view.

They are not considered drugs, there is lack of controlled studies stating their real efficacy.

There is lack of a shared regulation assessment.

Nutraceuticals: TORs.



Nutraceuticals: classification.

Neutraceuticals can be classified based on:

- Natural source
- Pharmacological conditions
- Chemical constitution



Nutraceuticals: classification.

Classification based on the chemical groups

s.no	Class	Examples
1	Inorganic mineral supplements	Minerals
2	Probiotics	Helpful bacteria
3	Prebiotics	Digestive enzymes
4	Dietary fibres	Fibres
5	Antioxidants	Natural antioxidants
6	Phytochemicals	
	Fatty acids	Omega 3 fatty acids
	Phenolics	Tea polyphenols
	Isoprenoids	carotenoids
	Lipids	Sphingolipids
	Proteins	soyaproteins
7	Herbs as functional food	--------

Nutraceuticals: classification.

Classification :based on their use in disease

condition	Nutraceuticals
Allergy relief	Ginkgo biloba
Arthritis support	glucosamine
Cancer prevention	Flax seeds ,green tea
Cholesterol lowering	garlic
Digestive support	Digestive enzymes
Diabetic support	Garlic,monordica
Female hormone support	Black cohosh
immunomodulator	ginseng
Prostate support	Tomato lycopenes

Nutraceuticals: food or drugs?

QUESTION placed at the European Commission E-000065/2011 (dr. Christian Muscardin) about the presence on the market of products, called "nutraceuticals", which, unlike normal dietary supplements, have the effects of preventing or reducing the risk of disease, especially degenerative of a particular structure or function of the organism.

• **ANSWER** given by Commissioner John Dalli on behalf of the European Commission, February 21, 2011:

• The term "nutraceutical" is not currently defined in Community legislation.

• These products, under the current legislation, should be classified as dietary supplements or following authorization for marketing as drugs.



Nutraceuticals: food or drugs?

Court of Justice of the European Union: medicine/drug food.

• if it is presented as having properties for treating or preventing disease in human beings (definition of "presentation");

• if it is to be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions (definition "by function").

Plant-based products marketed in the form of dietary supplements (vegetable origin similar to nutraceuticals) must comply with Directive 2002/46/EC on food supplements and Regulation (EC) n. 1924/2006 on the claims about the effects of nutrition and health foods.

If a product, taking into account all its characteristics, may fall within the definition of a medicinal product and the definition of a product covered by other Community legislation, apply the Directive 2001/83/EC revised by Directive 2004/27/EC (food and drugs nutraceuticals).



Nutraceuticals: where can be found.

An approximate number of about 30,000 phyto components have been identified in plants.

- Approximately 5,000-10,000 are present in plant foods of common use/consumption.

- Assuming 5 daily servings of fruits and vegetables, you ensure the intake of about 1.5 g / day of nutraceuticals phytocomponents.



Nutraceuticals: where can be found.

Food	Phytochemical(s)
Allium vegetables (garlic, onions, chives, leeks)	Allyl sulfides
Cruciferous vegetables (broccoli, cauliflower, cabbage, Brussels sprouts, kale, turnips, bok choy, kohlrabi)	Indoles/glucosinolates Sulfaforaphane Isothiocyanates/thiocyanates Thiols
Solanaceous vegetables (tomatoes, peppers)	Lycopene
Umbelliferous vegetables (carrots, celery, cilantro, parsley, parsnips)	Carotenoids Phthalides Polyacetylenes
Compositae plants (artichoke)	Silymarin



Nutraceuticals: where can be found.

Citrus fruits (oranges, lemons, grapefruit) Glucarates	Monoterpenes (limonene) Carotenoids
Other fruits (grapes, berries, cherries, apples, cantaloupe, watermelon, pomegranate)	Ellagic acid Phenols Flavonoids (quercetin)
Beans, grains, seeds (soybeans, oats, barley, brown rice, whole wheat, flax seed) Protease inhibitors	Flavonoids (isoflavones) Phytic acid Saponins
Herbs, spices (ginger, mint, rosemary, thyme, oregano, sage, basil, tumeric, caraway, fennel)	Gingerols Flavonoids Monoterpenes (limonene)
Licorice root Green tea Polyphenols	Glycyrrhizin Catechins



Nutraceuticals: where can be found.

Most Commonly Studied Phytochemicals

Food	Phytochemical(s)
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Nutraceuticals: therapeutic uses.

Prevention/Therapy using nutraceuticals.

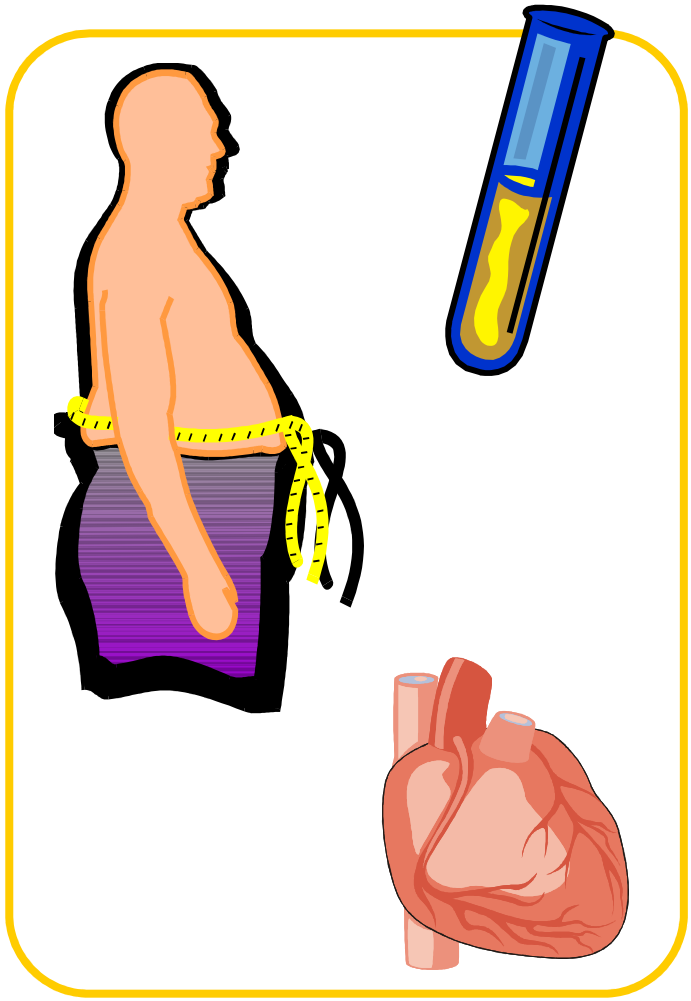
- Hypercholesterolemia
- Hypertension
- Type II diabetes
- Hypertryglyceridemia
- ……..

→ Metabolic syndrome

→ A nutraceutical pro active approach is possible?



Metabolic syndrome (SM): some data.



Van Gaal LF, et al. Lancet 2005;365:1389-97

50% of people from Europe are overweight

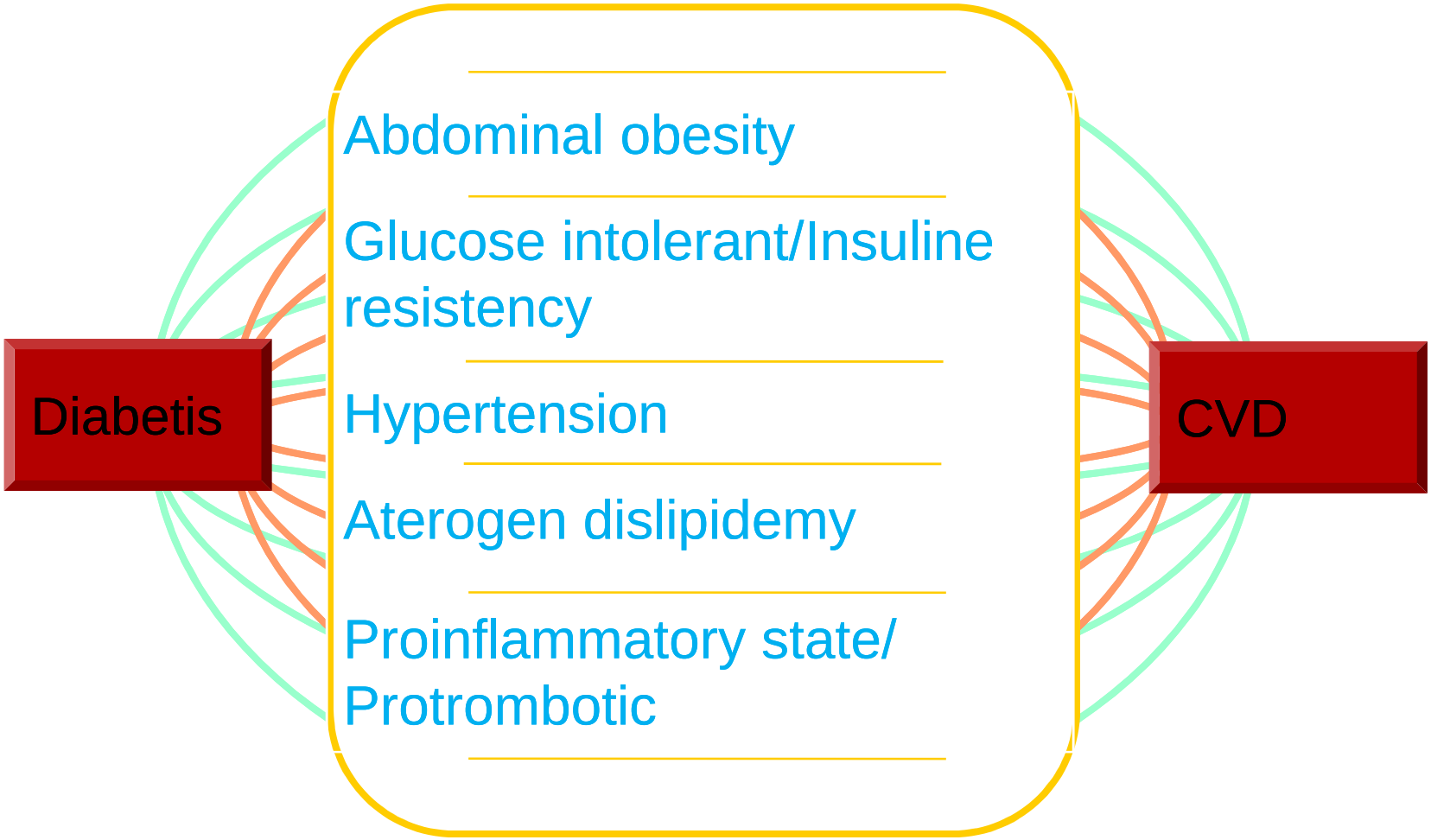
30% suffer from obesity

23-24% of USA suffer from SM

WHO estimated an about 2.5 millions of people dead worldwide due to overweight and to cardiovascular diseases

SM: ICD-9-CM code = 277.7

Metabolic syndrome “cluster” of risk factors.



National Cholesterol Educational Program (NCEP), Adult Treatment Panel (ATP) III; 2001

Metabolic syndrome.

Central obesity (european and north american population).

i. Waist circumference ≥ 94 cm (male) and ≥ 80 (female)

Together with at least **TWO** of the following:

ii. TG > 150 mg/dL or specific treatment

iii. CHDL < 40 mg/dL (male) e < 50 mg/dL (female) or specific treatment

iv. SBP ≥ 130 mmHg e/o DBP ≥ 85 mmHg or anti hypertension treatment

v. Glycemic index ≥ 100 mg/dL or a DM2 diagnosis



Therapeutic approach.

METABOLIC SYNDROME





ORGAN DAMAGE PRESENCE

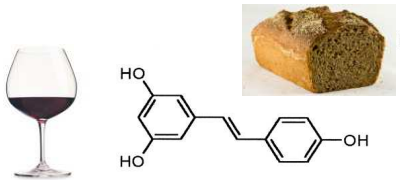
NO

YES

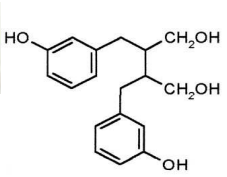
LYFESTYLE CHANGE
NUTRACEUTICALS

PHARMACOLOGIC THERAPY

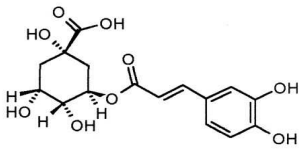
Monomeric and oligomeric phenols.



resveratrol
(stilbene)



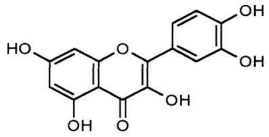
enterodiol
(lignan)



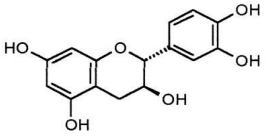
chlorogenic acid
(phenolic acid)







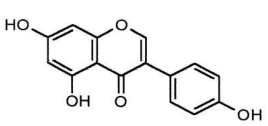
quercetin
(flavonol)



(+)-catechin
(flavanol)



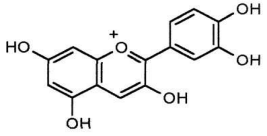




genistein
(isoflavone)



hesperetin
(flavanone)

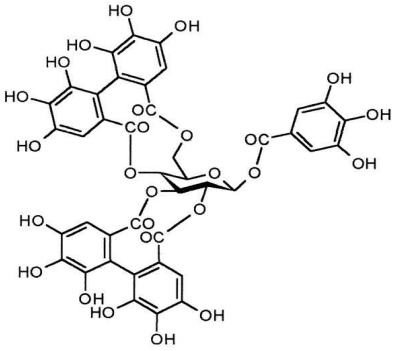


cyanidin
(anthocyanidin)

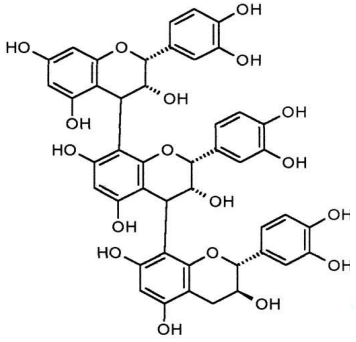








casuarictin
(ellagitannin)

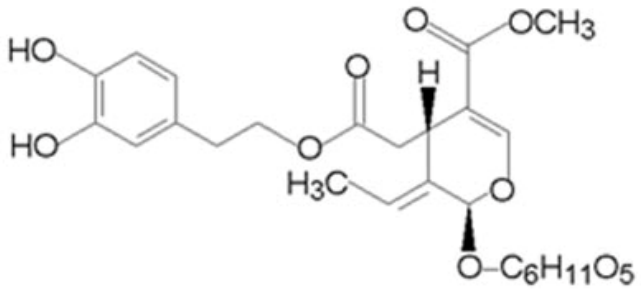


procyanidin trimer
(flavanol)

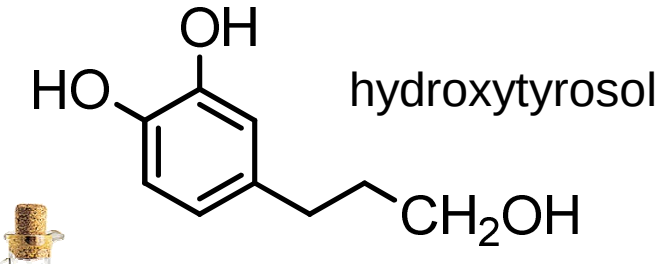


Catecolic derivatives.





oleuropein



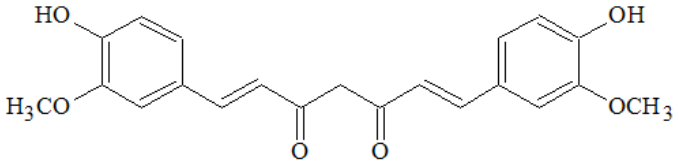
hydroxytyrosol





alkylresorcinols



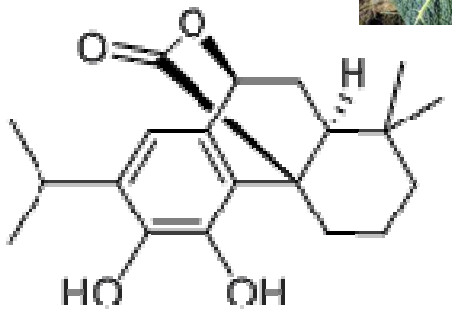


curcumin







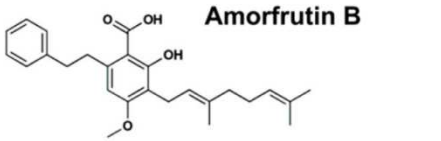


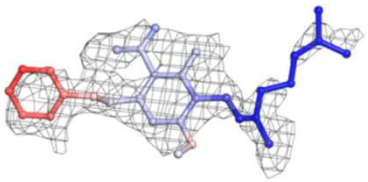
carnosol

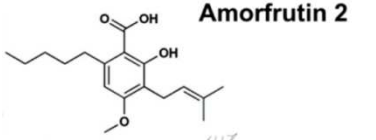
Resorcinic derivatives.

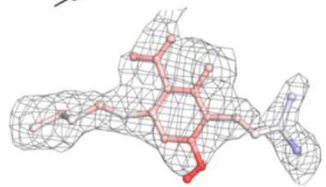


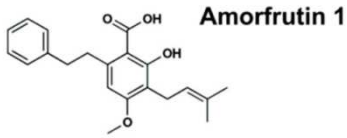
Amorpha fruticosa

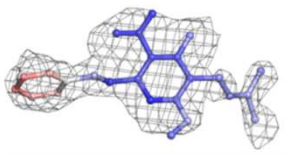








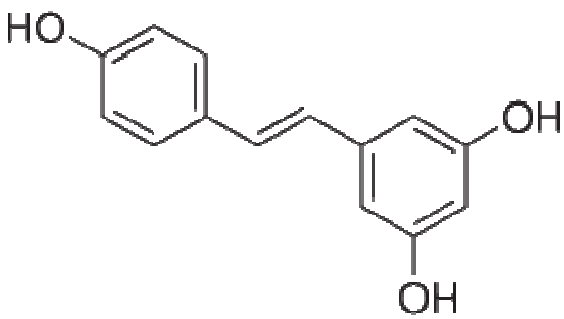






Liquorice

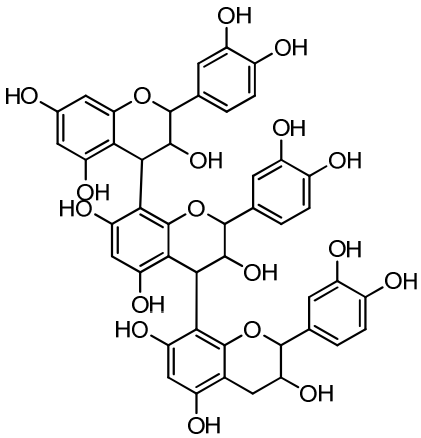
Resveratrol



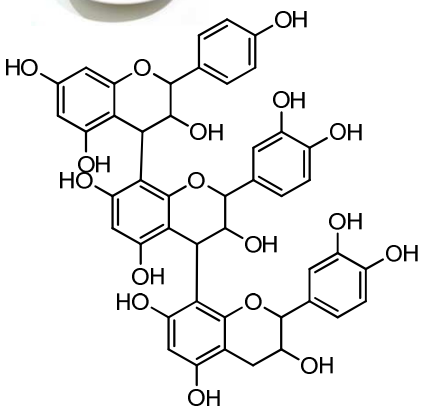


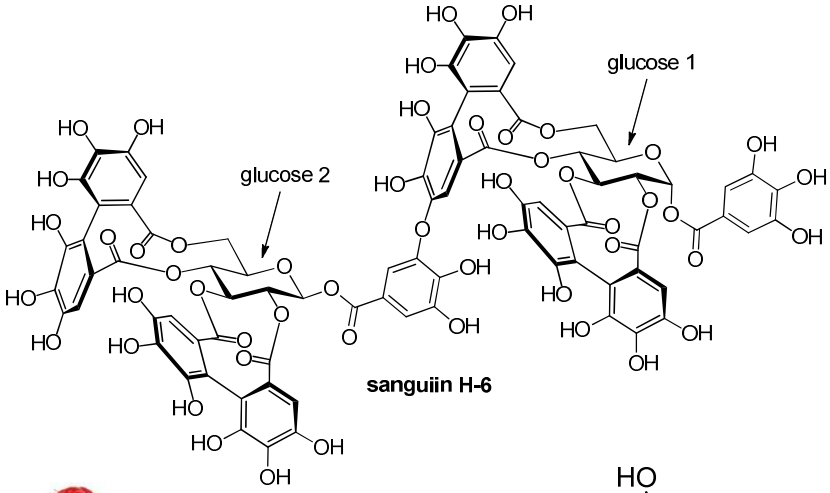
Tomatoes, grapes, cauliflower

Oligomeric polyphenols –Tannins.



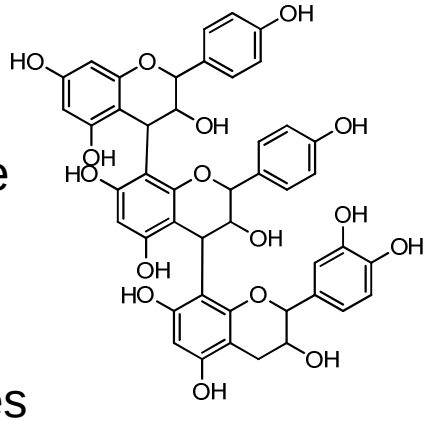








Apple





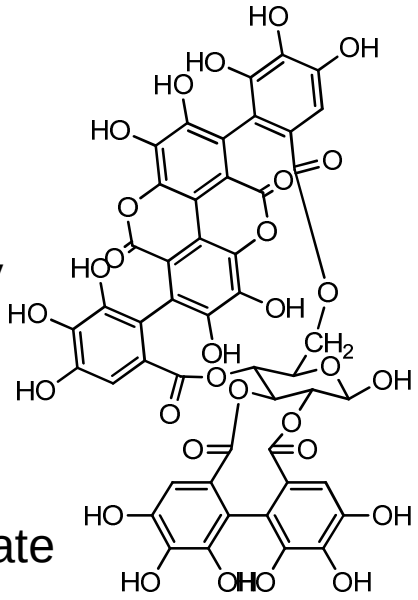
Dates



Raspberry



Pomegranate



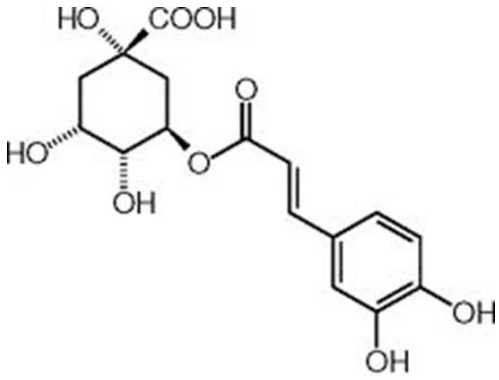
Nutraceuticals: possible uses.

An example.

The artichoke (Cynara scolymus) extract polyphenols: the main components are chlorogenic acid, caffeic acid and cynarin.

In year 1900 scientific research has focused on the properties hepatostimulants, hepatoprotective, choleretic and hypocholesterolemic associated to extracts of Cynara leaves, as advocated by medicine doctors already in year 1700.





chlorogenic acid

Nutraceuticals: possible uses.

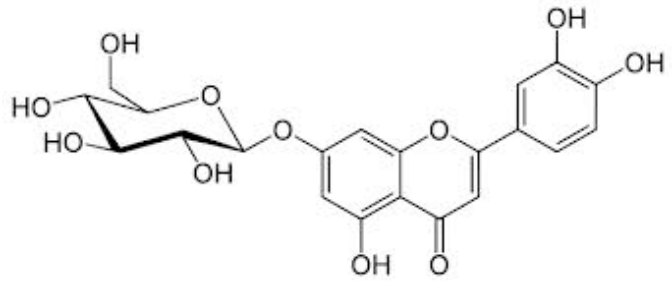
Artichoke: bioactive substances.

Chlorogenic acids

Cynara extracts

Flavanoids

- **5-O-caffeilchinic acid**
- **1,5-dicaffeilchinic acid**
- **caffeic acid**



- **Luteoline**
- **Cinaroside**
- **Scolimoside**

Nutraceuticals: possible uses.

Artichoke variety	mg chlorogenic acid/100g
***Romolo* stem**	**27,826**
***Romolo* head**	**6,276**
***Romolo* leaves**	**0,5**



Anti oxidant activity:

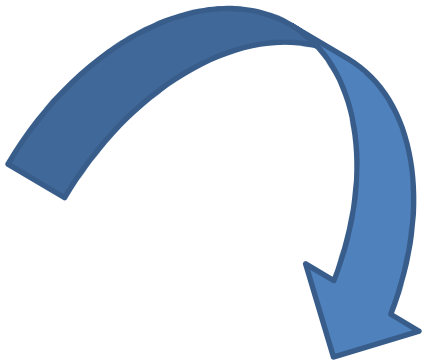
Artichoke variety	Total phenolic content mg AGE/100g	DPPH µmol TE/100g	FRAP µmol TE/100g
***Romolo* stem**	**21,35**	**78,61**	**104,46**
***Romolo* head**	**4,53**	**38,95**	**24**
***Romolo* leaves**	**26,44**	**124,47**	**64,54**

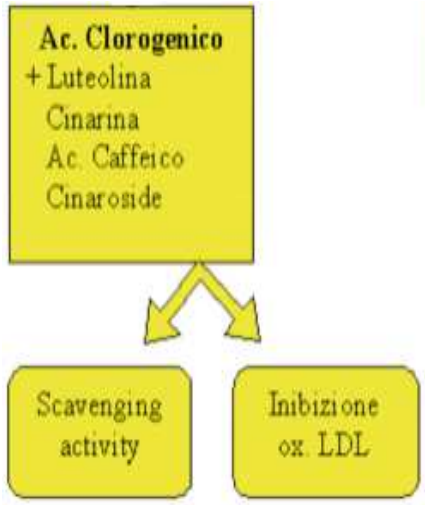
Nutraceuticals: recovery/uses.

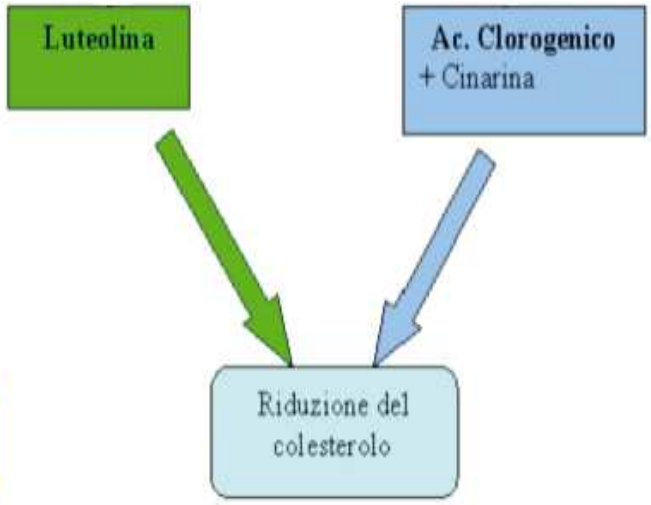
Sustainable use of industrial wastes.











Bioactive molecules rich sources



Nutraceuticals: possible uses.

Cholesterol-lowering action of artichoke extracts.

1. increased choleresis and then increased excretion of salts and bile acids rich in cholesterol;
2. inhibition of cholesterol biosynthesis.

- Cholesterol is synthesized in the liver from acetyl-CoA and released in plasma.
- The extent of hepatic biosynthesis is controlled by the intracellular concentration of cholesterol.

Nutraceuticals: possible uses.

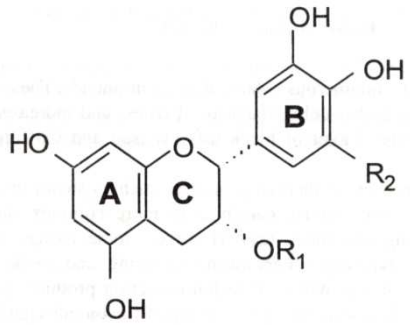
Green tea: functional food/nutraceutical



Obtained from a plant: *Camellia sinensis (L.).*

The freshly harvested leaves are immediately processed to inactivate the enzymatic oxidation process.

- Green tea has the highest concentration of polyphenols than other types of tea.
- Green tea has **hypoglycemic properties**.



catechine	R_1	R_2
EGCG	Gallato	OH
ECG	Gallato	H
EGC	H	OH
EC	H	H



Nutraceuticals: possible uses.

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Food Chemistry

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

In vitro hypoglycaemic and hypolipidemic potential of white tea polyphenols

Gian Carlo Tenore[a,*], Paola Stiuso[b], Pietro Campiglia[c], Ettore Novellino[a]

[a] Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Napoli, Italy
[b] Department of Biochemistry and Biophysics, Second University of Naples, Napoli, Italy
[c] Department of Pharmaceutical and Biomedical Sciences, University of Salerno, Via Ponte Don Melillo, 1, 84084 Salerno, Italy



Tè Bianco



Tè Verde



Tè Nero

Nutraceuticals: possible uses.

Catechins neuro protective role**.**



Review

NEURO-SIGNALS

Neurosignals 2005;14:45–60
DOI: 10.1159/000085985

Multifunctional Activities of Green Tea Catechins in Neuroprotection

Modulation of Cell Survival Genes, Iron-Dependent Oxidative Stress and PKC Signaling Pathway

Silvia A. Mandel Yael Avramovich-Tirosh Lydia Reznichenko Hailin Zheng
Orly Weinreb Tamar Amit Moussa B.H. Youdim



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Journal of Nutritional Biochemistry

REVIEWS: CURRENT TOPICS

Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration

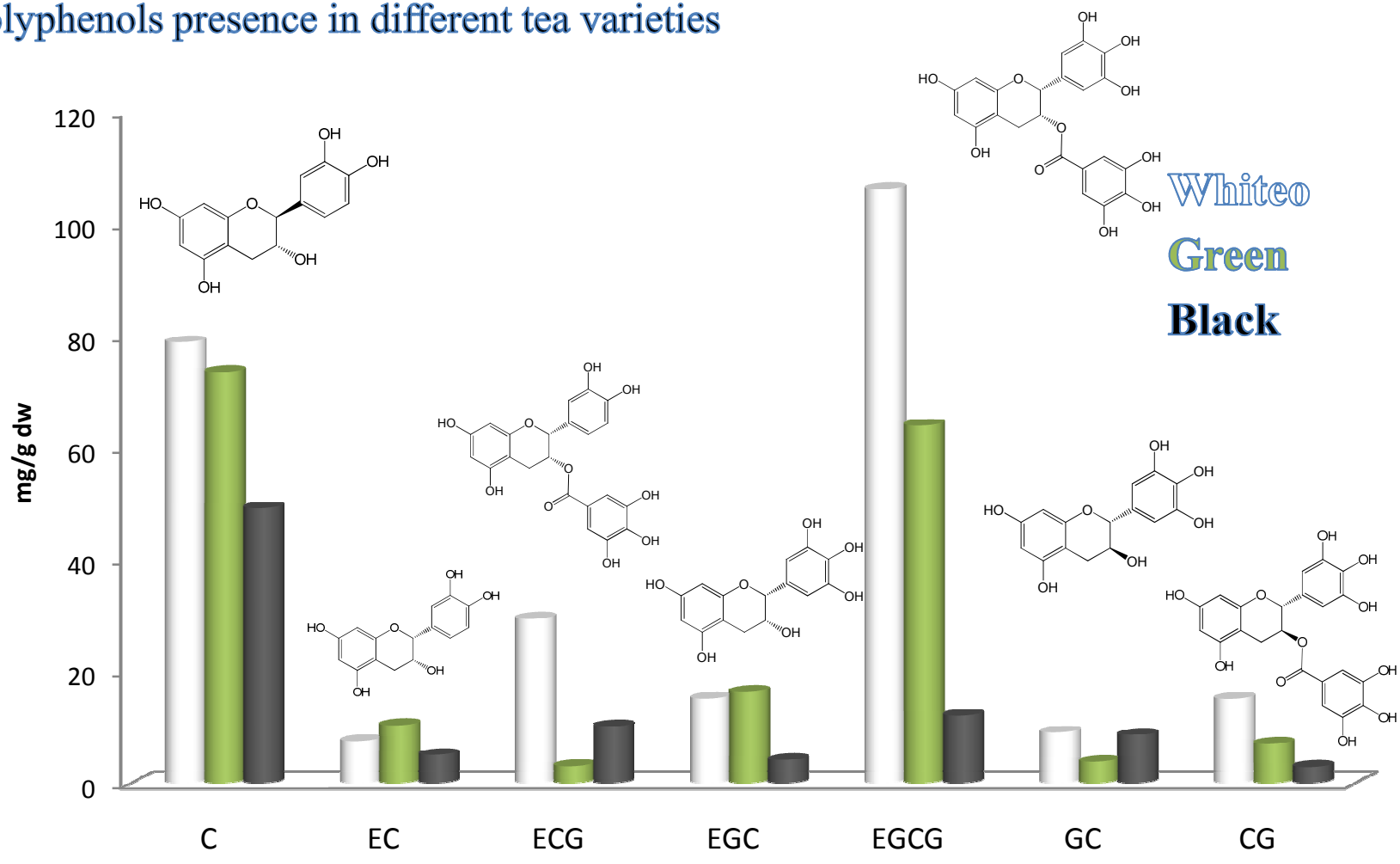
Brad A. Sutherland, Rosanna M.A. Rahman, Ian Appleton*

Department of Pharmacology and Toxicology, University of Otago, Dunedin, P.O. Box 913, Dunedin, New Zealand

Received 14 September 2005; accepted 11 October 2005

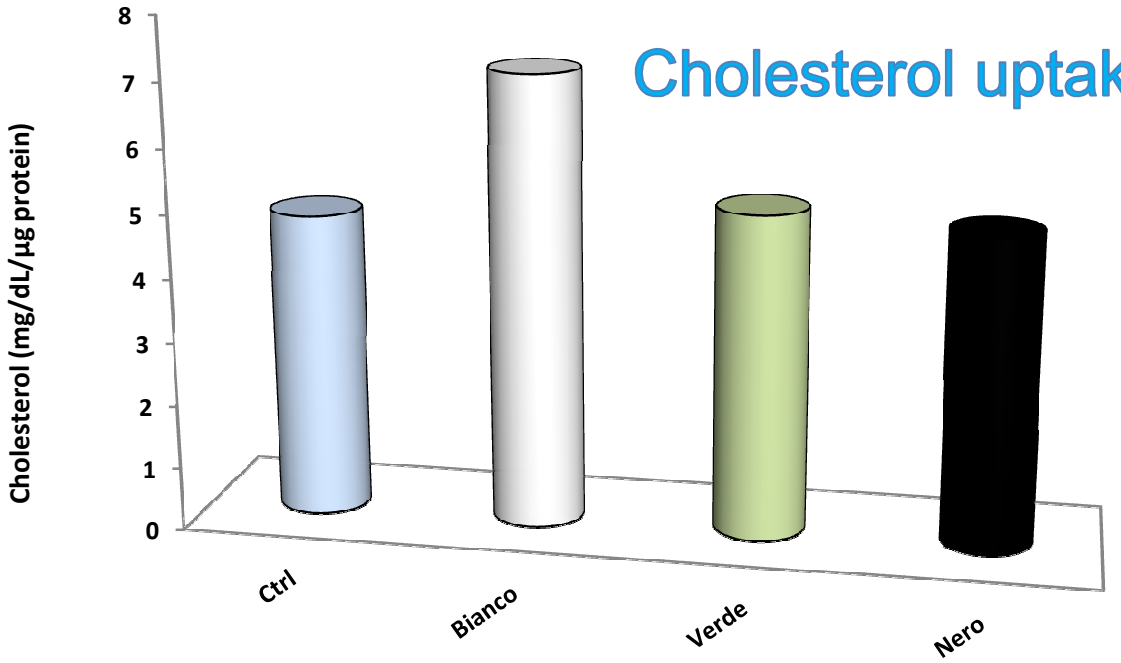
Nutraceuticals: possible uses.

Polyphenols presence in different tea varieties

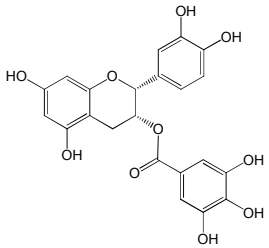


C = (-)-Catechina
EC = (-)-Epicatechina
ECG = (-)-Epicatechingallato
EGC = (-)-Epigallocatechina
EGCG = (-)-Epigallocatechingallato
GC = (-)-Gallocatechina
CG = (-)-Catechingallato

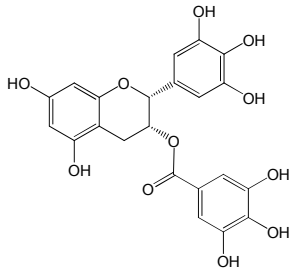
Nutraceuticals: possible uses.



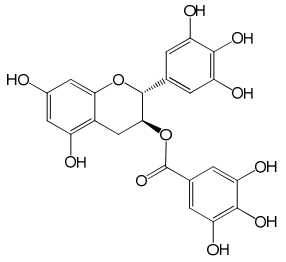
Main responsible matobolites



ECG = (-)-Epicatechingallato

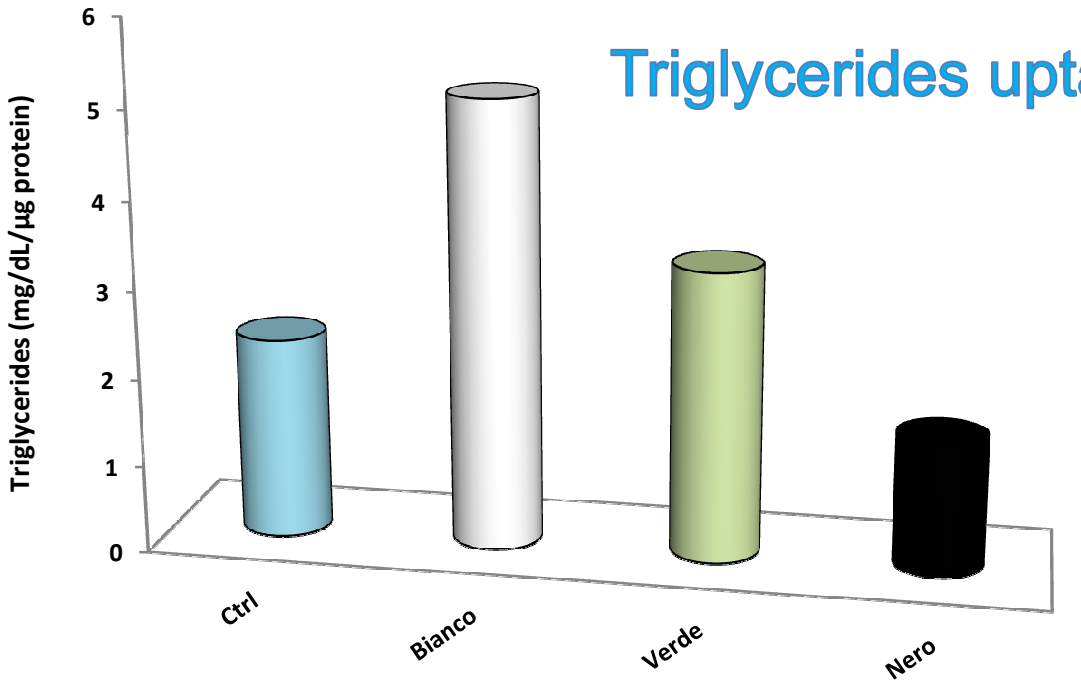


EGCG = (-)-Epigallocatechingallato

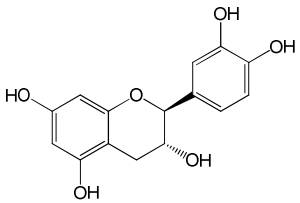


CG = (-)-Catechingallato

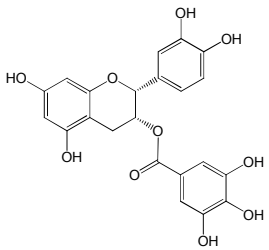
Nutraceuticals: possible uses.



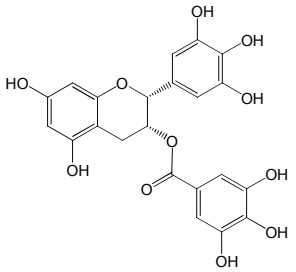
Main responsible metabolites



C = (-)-Catechina



ECG = (-)-Epicatechingallato

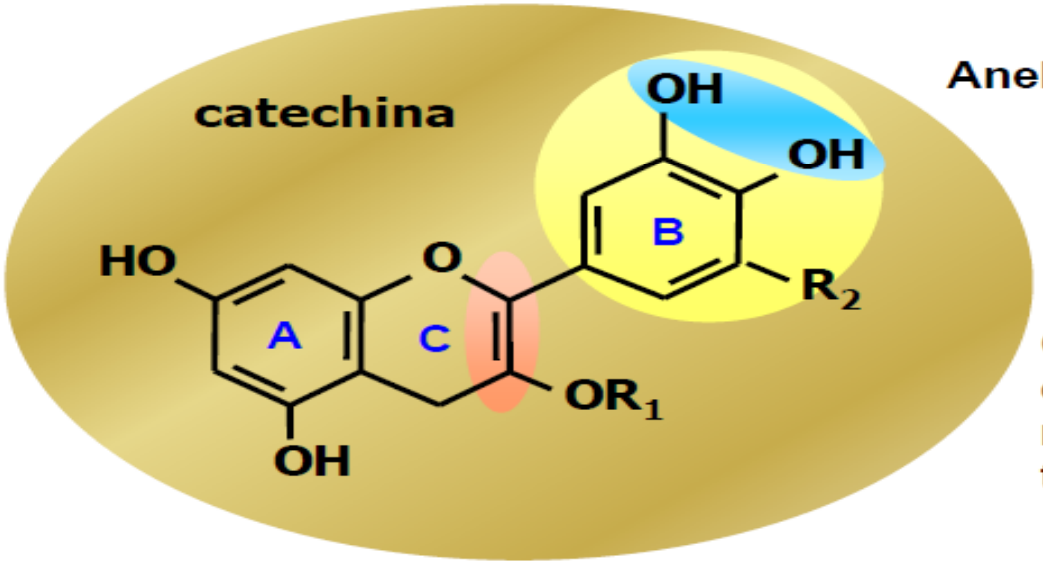


EGCG = (-)-Epigallocatechingallato

Nutraceuticals: possible uses.

Catechins: antioxidant action.

Proprietà Antiossidanti Classiche:



Anello B catecolico

Insaturazione nell'anello C

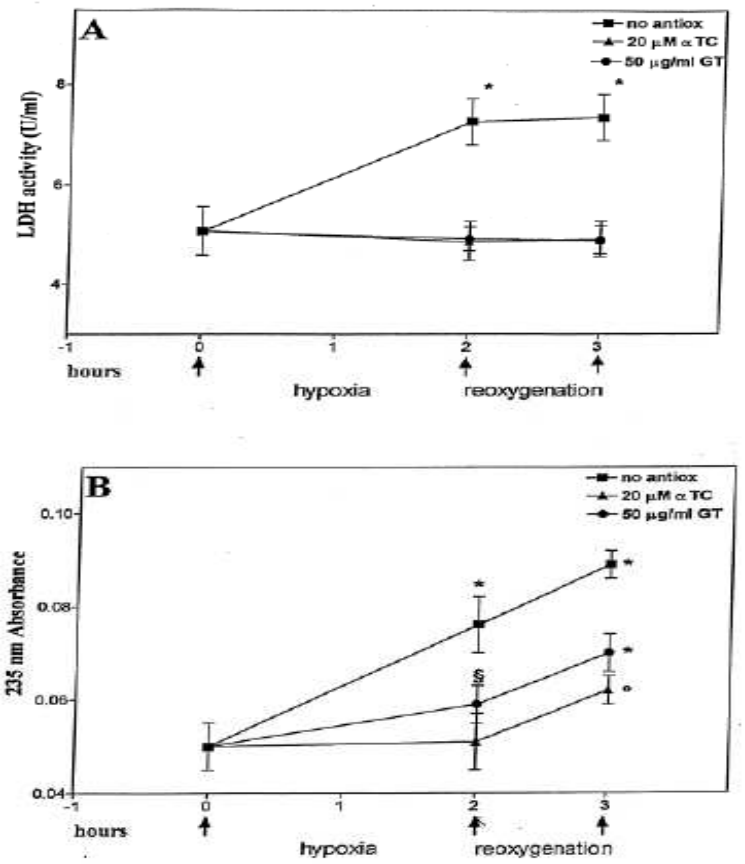
Gruppi in grado di chelare ioni di metalli di transizione

Potenti scavengers di ROS e RNS

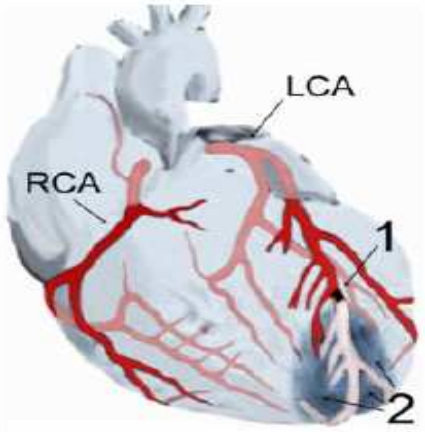
- Ruolo chemiopreventivo
- Ruolo cardioprotettivo
- Ruolo neuroprotettivo

Nutraceuticals: possible uses.

Catechins: cardio protective role.



Nei confronti del danno da ipossia riossigenazione indotto nella cellula cardiaca



S. Hrelia et al. J. Nutr. Biochem. 13, 103-111 (2002)

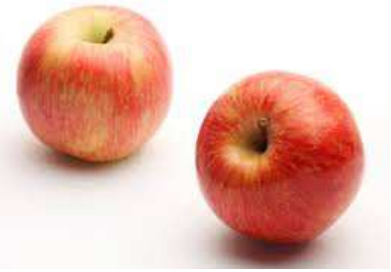
Nutraceuticals: possible uses.

Apple: an *in se* functional food ?

I. Significant source of phytocompounds (flavonoids) among which quercetin (5 - 15 mg / 100 g) is the main one.
II. Contains antioxidant polyphenols with proven efficacy.
III. Apple extracts inhibit the cholesterol uptake.
IV. The effect on the organism is similar to statins.

Apple: → extract → **nutraceutic**



Nutraceuticals: possible uses.

Contents lists available at SciVerse ScienceDirect

Food Chemistry

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

Nutraceutical potential of polyphenolic fractions from Annurca apple (*M. pumila* Miller cv Annurca)

Gian Carlo Tenore [a,*], Pietro Campiglia [b], Paola Stiuso [c], Alberto Ritieni [a], Ettore Novellino [a]

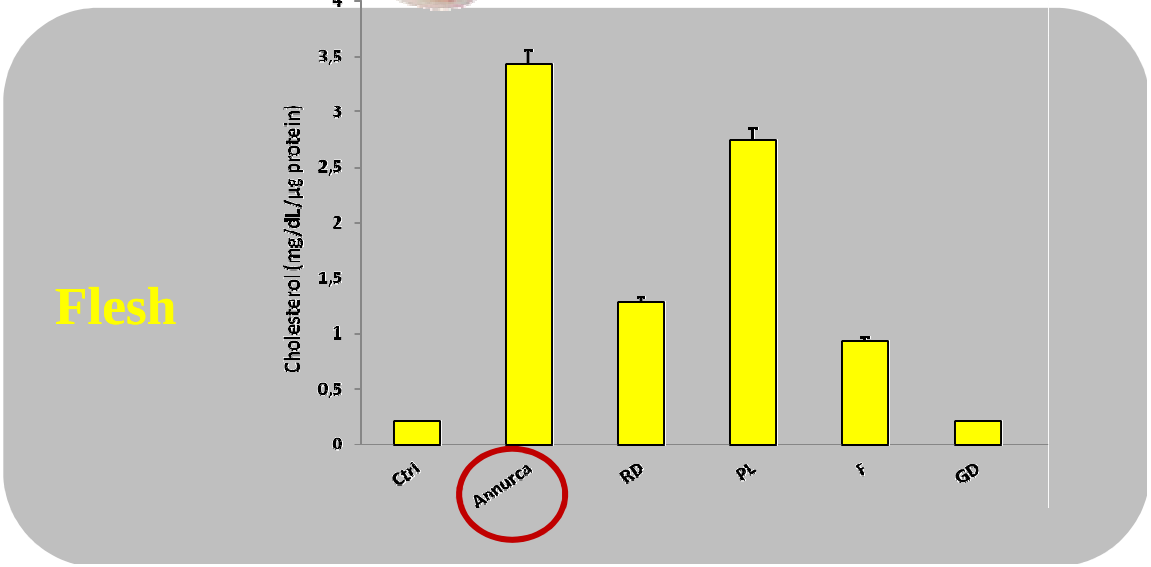
[a] Department of Medicinal Chemistry, Università di Napoli Federico II, Via D. Montesano 49, 80131 Napoli, Italy
[b] Department of Pharmaceutical and Biomedical Sciences, University of Salerno, Via Ponte Don Melillo, 1, 84084 Salerno, Italy
[c] Department of Biochemistry and Biophysics, Second University of Naples, Napoli, Italy







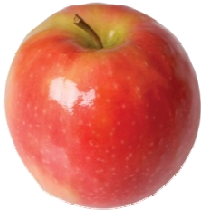
Cholesterol uptake inhibition.



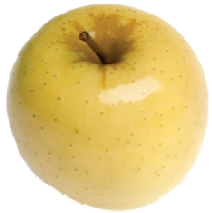
Nutraceuticals: possible uses.


Annurca

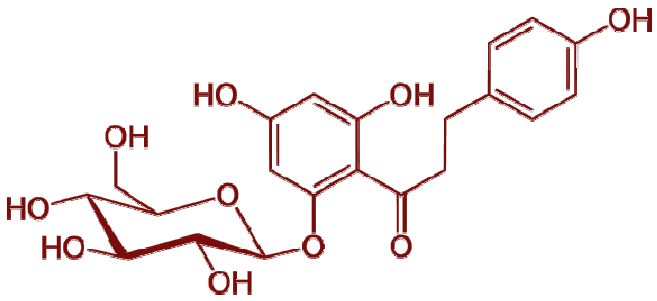

Red Delicious


Pink Lady

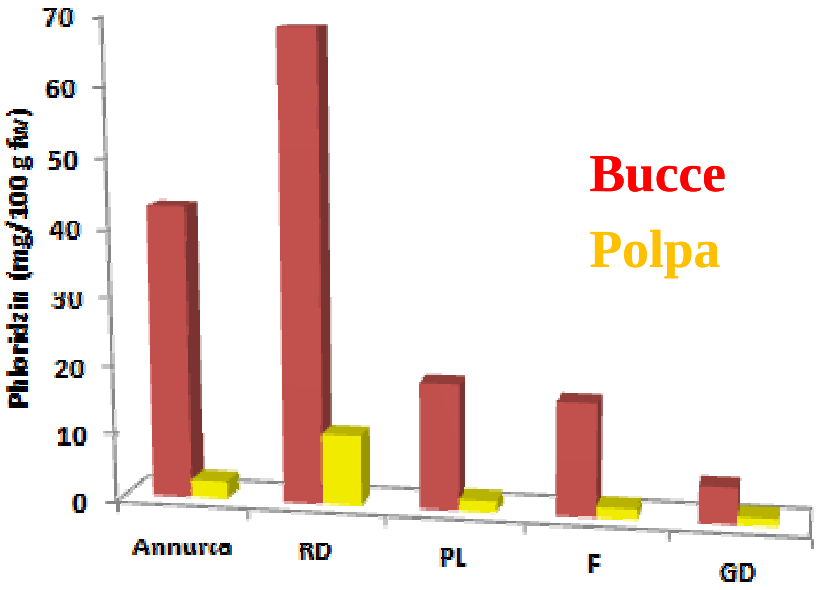

Fuji


Golden Delicious

Hypoglicemic metabolite/agent



Florizine



Nutraceuticals: possible uses.



Annurca



Red Delicious



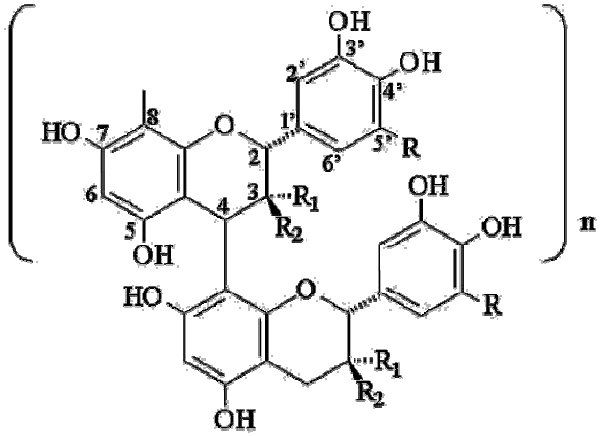
Pink Lady



Fuji

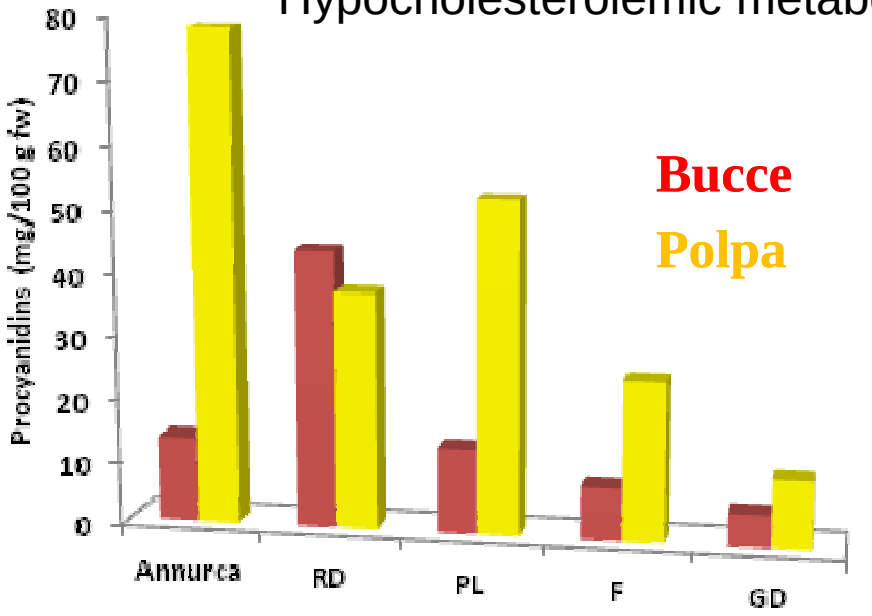


Golden Delicious



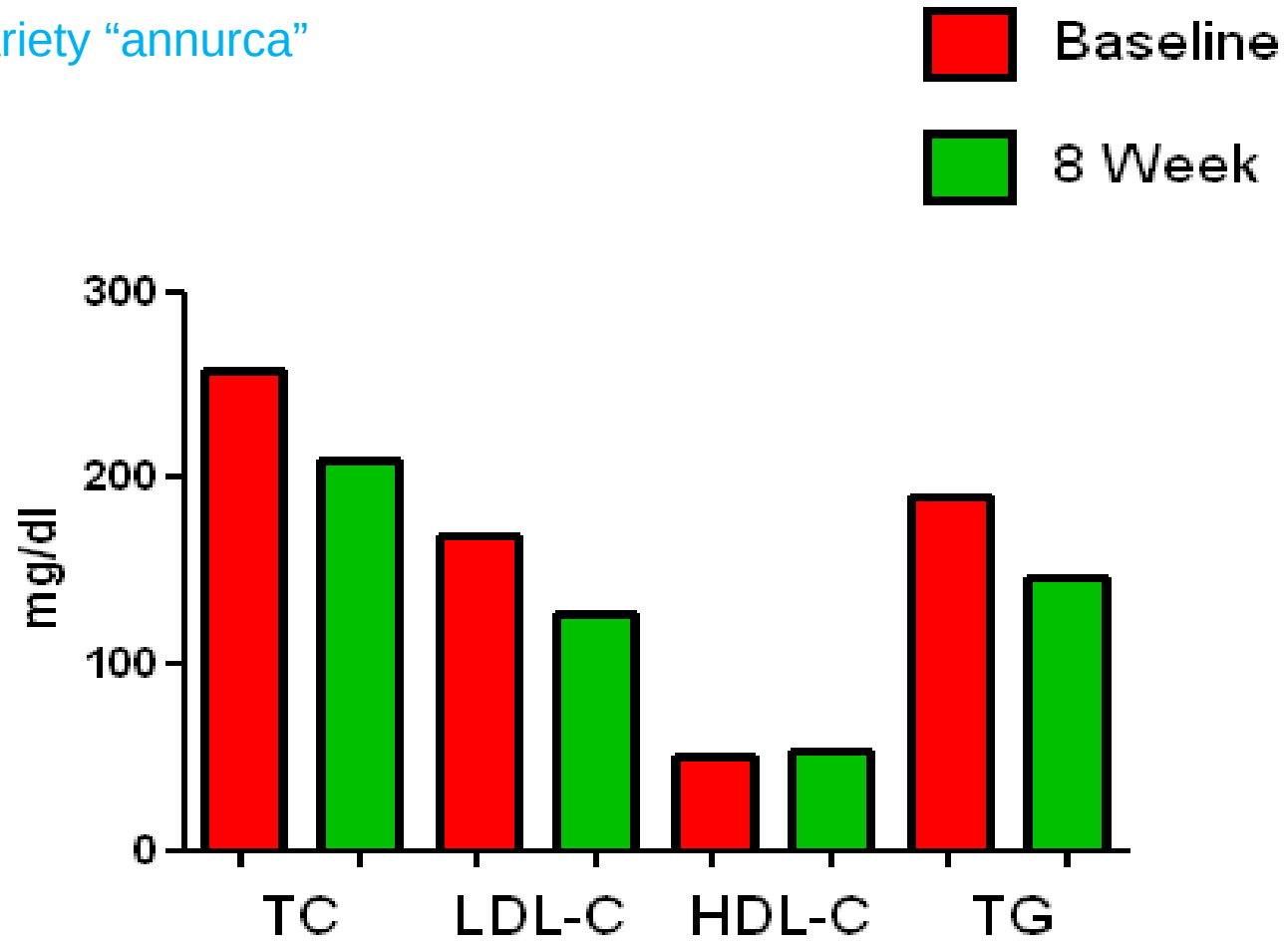
Oligomeric procyanidins

Hypocholesterolemic metabolites



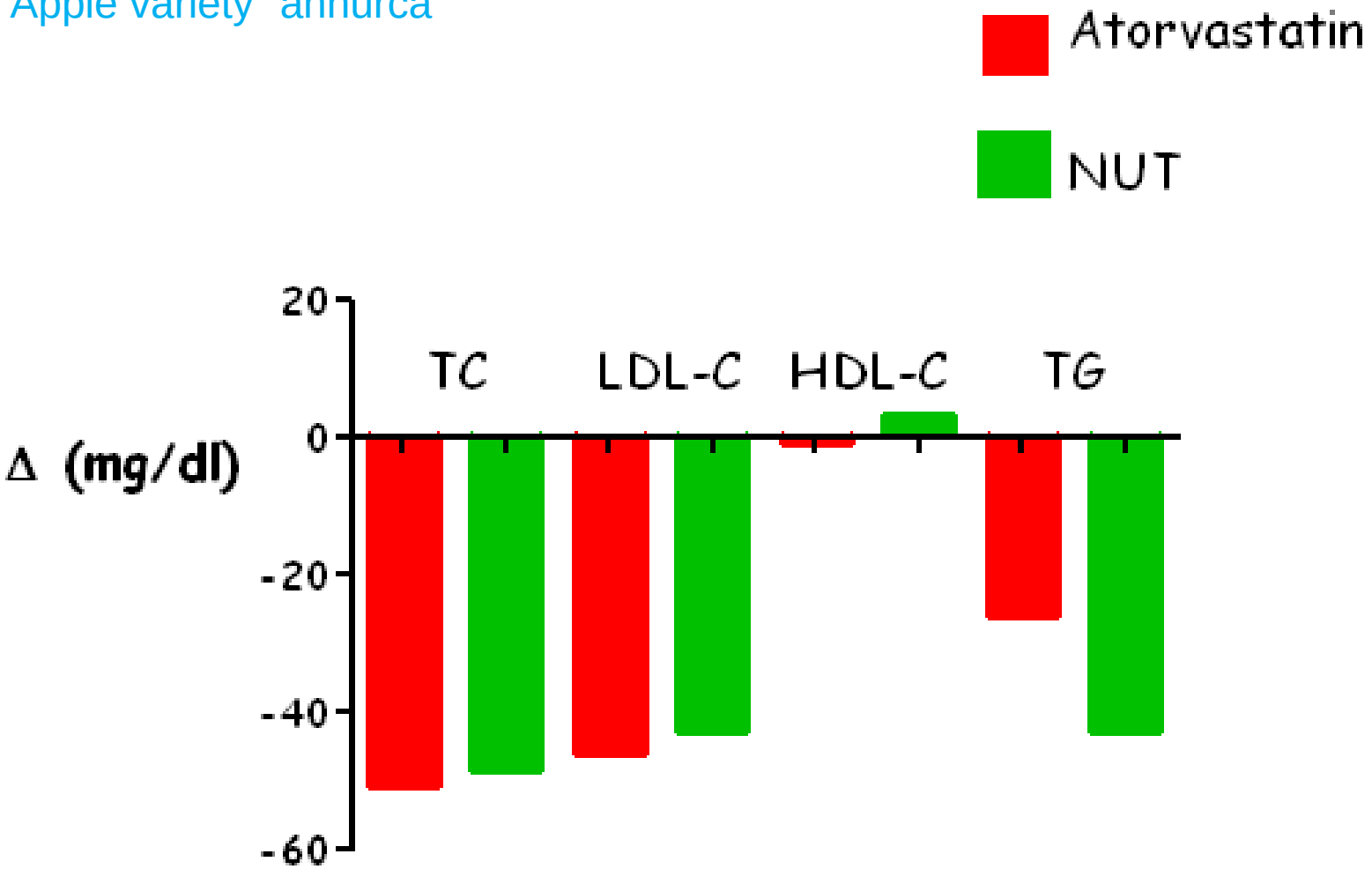
Nutraceuticals and metabolic syndrome.

Apple variety “annurca”



Lipidic profile in patients treated with atorvastatin v/s nutraceutical (NUT)

Apple variety “annurca”



Nutraceutic potential of grape polyphenols.





Flavonols
Antocianins

Pro-antocyanidins

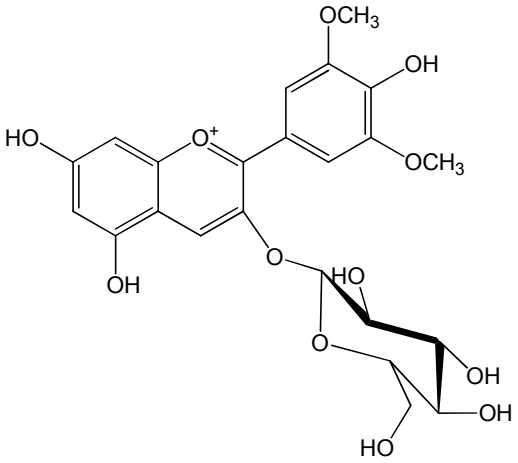
"Antioxidant protection of the cardiovascular system"

Shao et al. (2006). **Grape seed proanthocyanidin extract attenuates oxidant injury in cardiomyocytes**. *Pharmacological Research*

Poliphenols content: juice > wine > grape/fruits

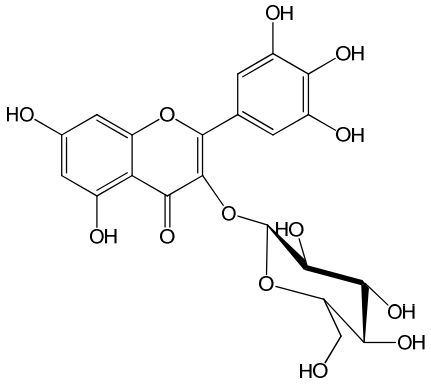
Main active molecules.

Antocianins

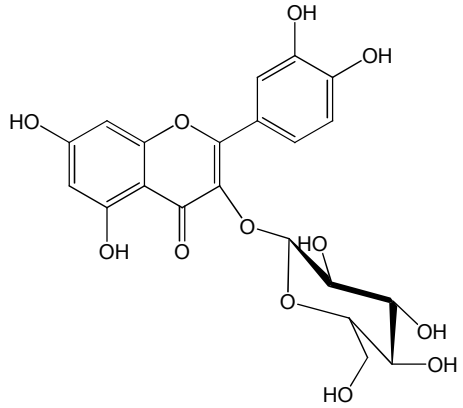


Malvidin-3-O-glucoside
114 mg/100 mL
35% anthocyanins

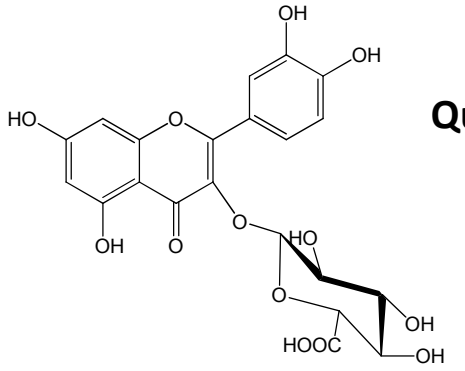
Flavonols



Myricetin-3-O-glucoside
93 mg/100 mL
27% flavonols



Quercetin-3-O-glucoside
80 mg/100 mL
23% flavonols



Quercetin-3-O-glucuronide
76 mg/100 mL
22% flavonols

Main active molecules.

Polyphenolic profile

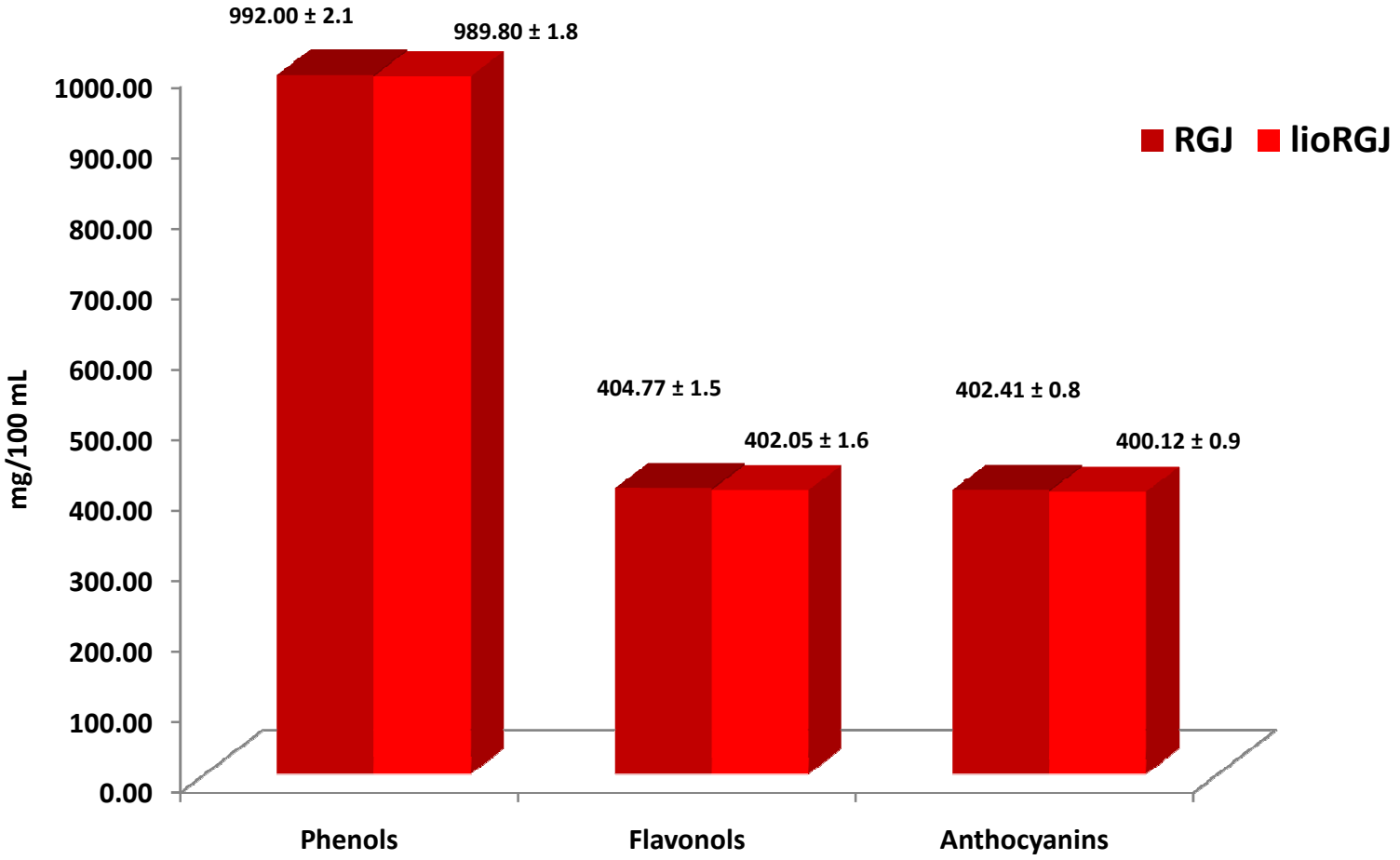
Antocianins

Peak	Compound	mg ME/100 mL*	
		RGJ	lioRGJ
1	Delphinidin-3-O-glucoside	34.78 ± 1.1	34.87 ± 1.3
2	Cyanidin-3-O-glucoside	21.63 ± 1.2	21.63 ± 1.1
3	Petunidin-3-O-glucoside	25.63 ± 1.4	25.68 ± 1.0
4	Peonidin-3-O-glucoside	31.24 ± 1.0	31.15 ± 0.9
5	Malvidin-3-O-glucoside	114.63 ± 1.9	114.50 ± 1.7
6	Delphinidin-3-O-acetylglucoside	10.38 ± 1.5	10.40 ± 0.3
7	Cyanidin-3-O-acetylglucoside	5.08 ± 0.9	5.01 ± 0.4
8	Malvidin-3-(6-O-coumaroyl)glucoside (cis isomer)	12.38 ± 0.8	12.21 ± 0.4
9	Malvidin-(6-O-caffeoyl)glucoside	52.99 ± 1.2	53.00 ± 0.6
10	Peonidin-3-(6-O-coumaroyl)glucoside (trans isomer)	4.32 ± 1.0	4.32 ± 0.2
11	Malvidin-3-(6-O-coumaroyl)glucoside (trans isomer)	14.66 ± 0.8	14.35 ± 0.1

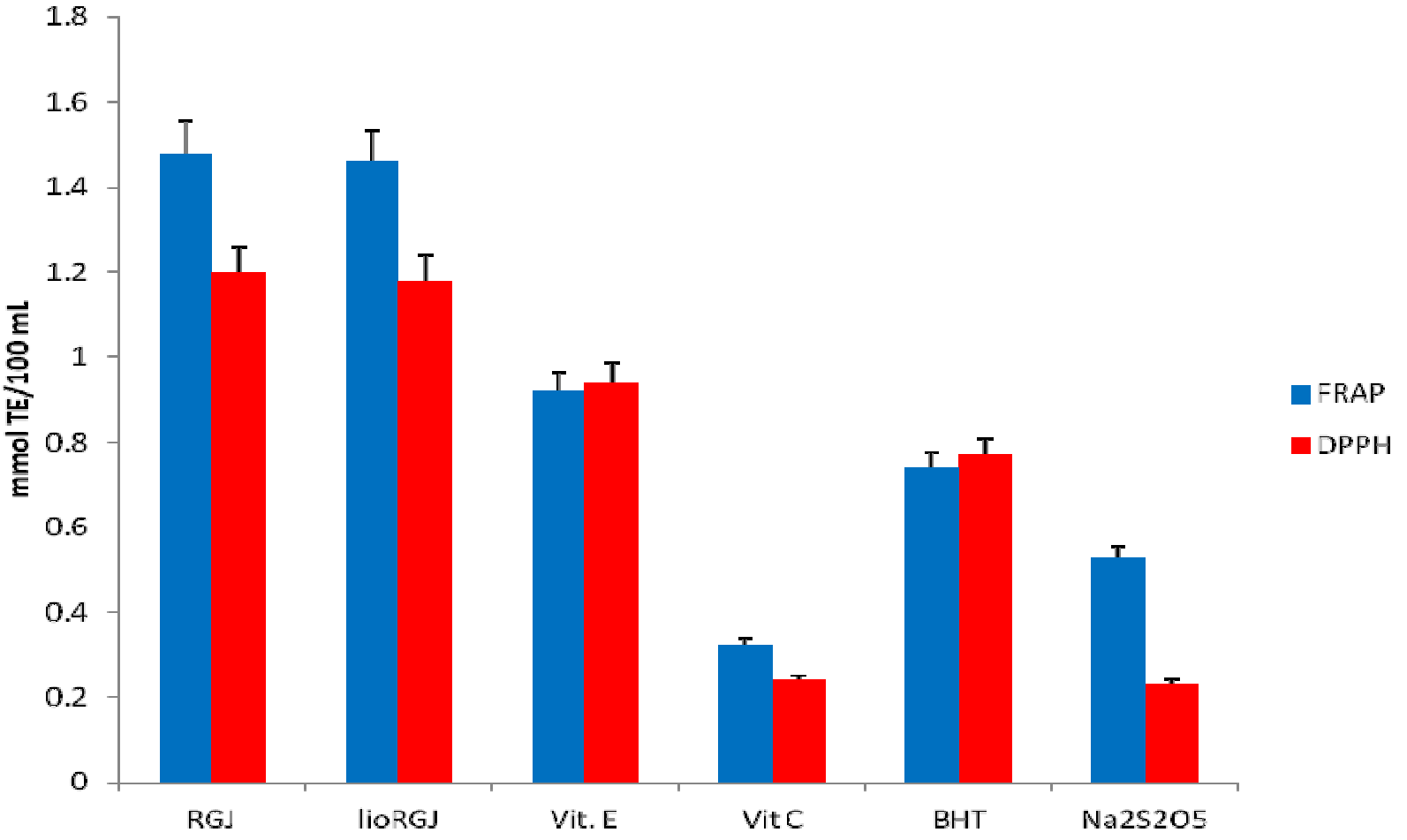
Flavonols

Peak	Compound	mg QE/100 mL*	
		RGJ	lioRGJ
1	Myricetin-3-O-glucoside	93.1 ± 0.3	91.7 ± 0.2
2	Quercetin-3-O-glucuronide	75.6 ± 0.2	73.5 ± 0.3
3	Quercetin-3-O-glucoside	79.8 ± 0.07	78.4 ± 0.08
4	Laricitrin-3-O-galactoside	13.3 ± 0.08	11.9 ± 0.06
5	Kaempferol-3-O-glucoside	5.6 ± 0.02	5.6 ± 0.01
6	Laricitrin-3-O-rhamnose-7-acid	18.2 ± 0.1	16.8 ± 0.2
7	Kaempferol-3-O-caffeoylate	16.8 ± 0.02	16.8 ± 0.02
8	Isorhamnetin-3-O-glucoside	24.5 ± 0.03	23.1 ± 0.04
9	Syringetin-3-O-galactoside	19.6 ± 0.05	20.3 ± 0.03

Red grape juice poliphenolic content before (RGJ) and after lyophilization (lioRGJ).



Antioxidant activity of red grape juice before (RGJ) and after lyophilization (lioRGJ)



FRAP = Antiradical indirect power
DPPH = Antiradical direct power

Nutraceutical potential of grape polyphenols.

"Antioxidant profile and *in vitro* cardiac radical-scavenging *vs* pro-oxidant effects of commercial red grape juices (*Vitis vinifera* L. cv. Aglianico N.)"

Gian Carlo Tenore, Michele Manfra, Paola Stiuso, Luigi Coppola, Mariateresa Russo, Isabel Maria Gomez Monterrey, Pietro Campiglia

***Journal of Agricultural and Food Chemistry,* 2012**





Nutraceutical potential of grape polyphenols.

Grape juice:

"*Functional food → Nutraceutic potential*"



Possible use as nutraceutical:

Support for the treatment of neoplastic diseases.

(Jones et al., Int. J. Cancer Res., 10(1), 46-53, 2014)

Hyperglicemy: a new therapeutic approach.

PPARγ (proliferator-activated receptor gamma) a nuclear receptor has a primary role in lipid and carbohydrates metabolism.

Problem: PPARγ-targeting drugs are characterized by unwanted side effects.

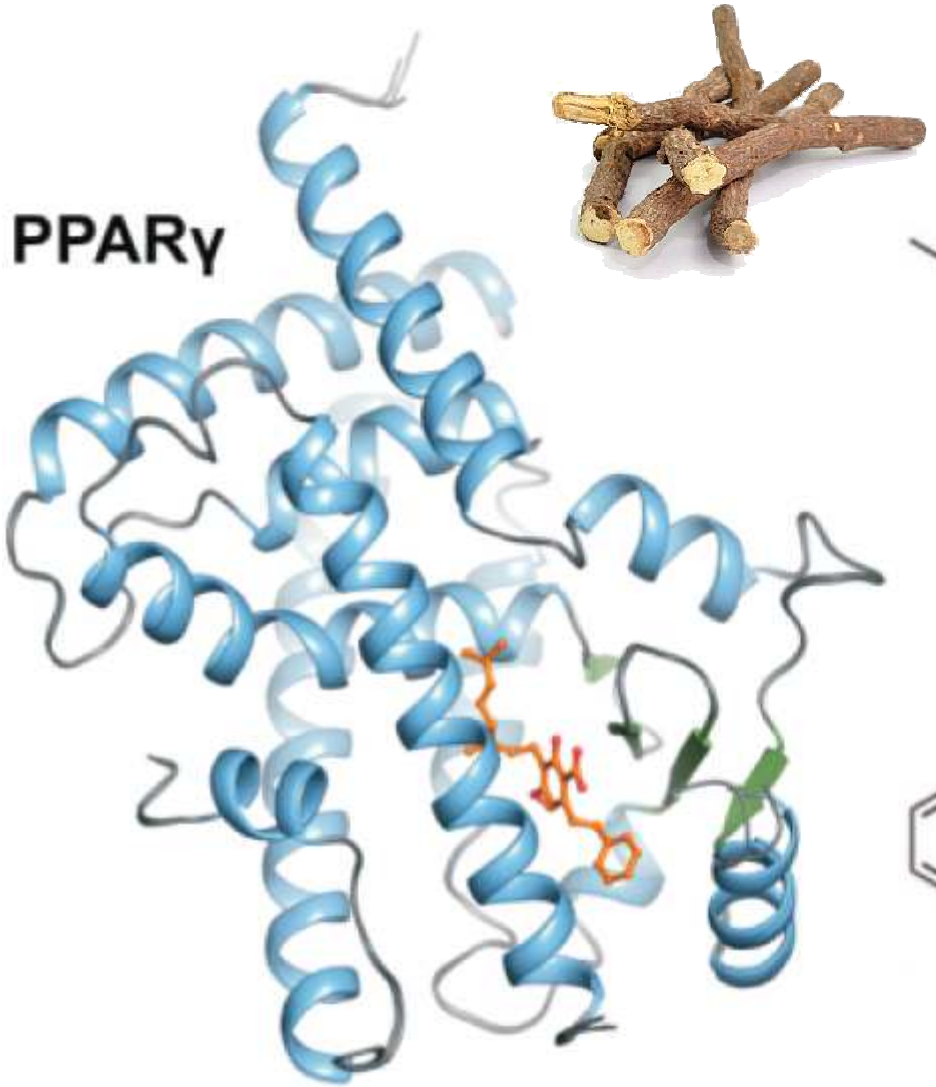
Natural products from edible biomaterials are a structurally different resource to easy the complex side effects of common use drugs.
It can be adopted a nutritional tailored approach to easy side unwanted effetcts.

Amorfrutins, extracted from the edible part of two legumes, namely *Glycyrrhiza foetida* and *Amorpha fruticosa*, are new and potent anti diabetes agents.

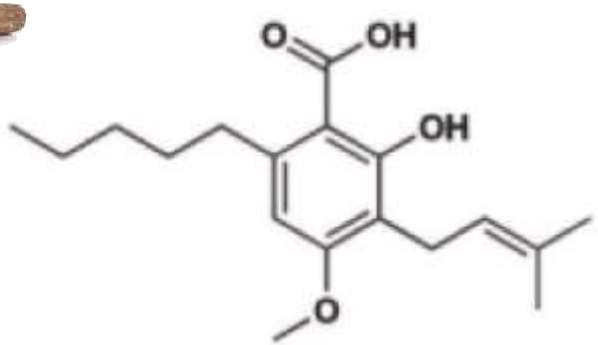
They selectively bond to the PPARγ receptor and activate it.



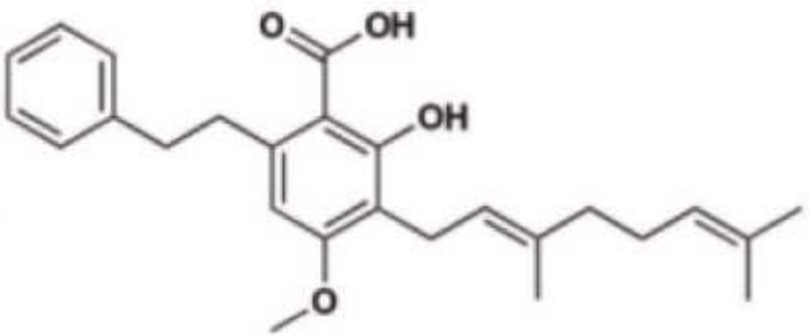
Hyperglicemy.



Amorfrutin 2



Amorfrutin B



Pro active nutraceutical approach: when and where?



"Beyond diet, before drugs"
(E. Novellino, 2012)

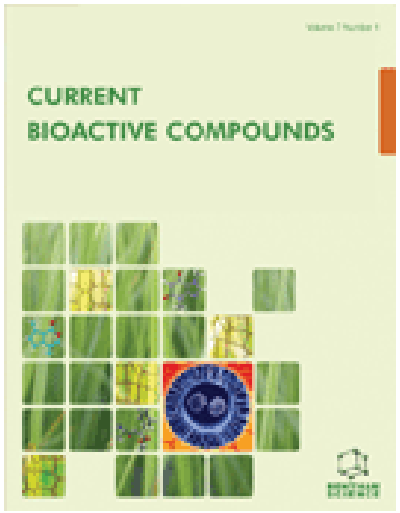




A. Santini, Journal of Food Research, 2014, (4), 1-5.

Pro active nutraceutical approach: when and where?

"Beyond diet, before drugs"
(E. Novellino, 2012)



Antonello Santini and Ettore Novellino
Current Bioactive Compounds, 2014, 10(1), 1-12.

