

LA PREVENZIONE DEL RISCHIO CARDIOVASCOLARE: UN APPROCCIO NON ORMONALE

PAOLA VILLA

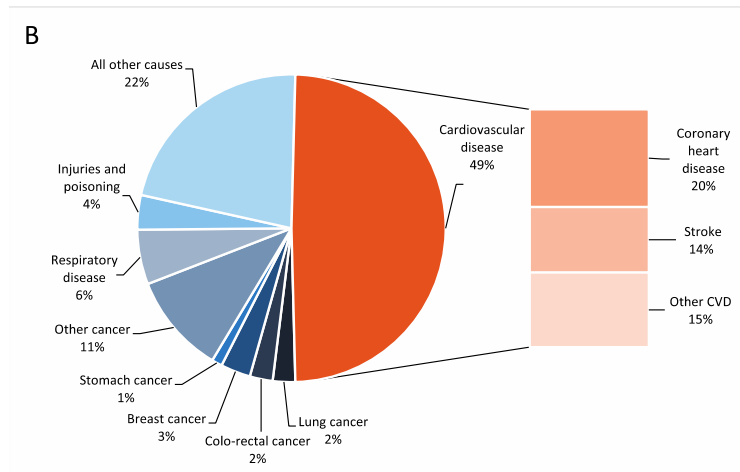
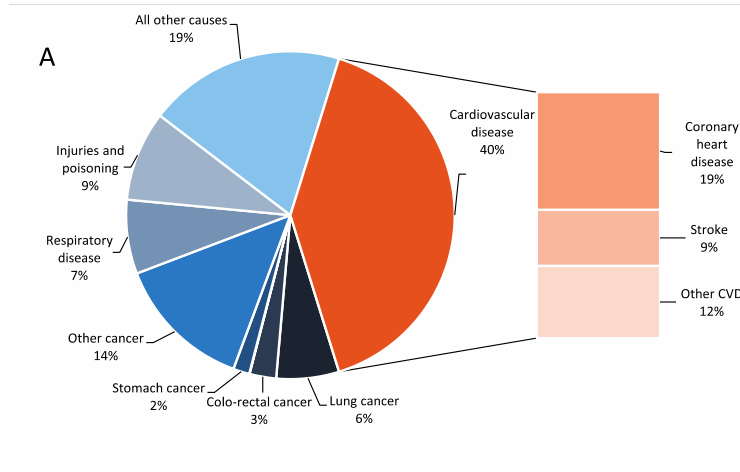
Dipartimento Scienze Della Salute Della Donna
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Fondazione Policlinico Universitario A. Gemelli
IRCCS
Universita' Cattolica Del Sacro Cuore
Roma

*La menopausa
da un'altra
prospettiva*



Foto: Arte de Nina Millen

CARDIOVASCULAR DISEASE IS THE NUMBER ONE KILLER OF WOMEN WORLDWIDE

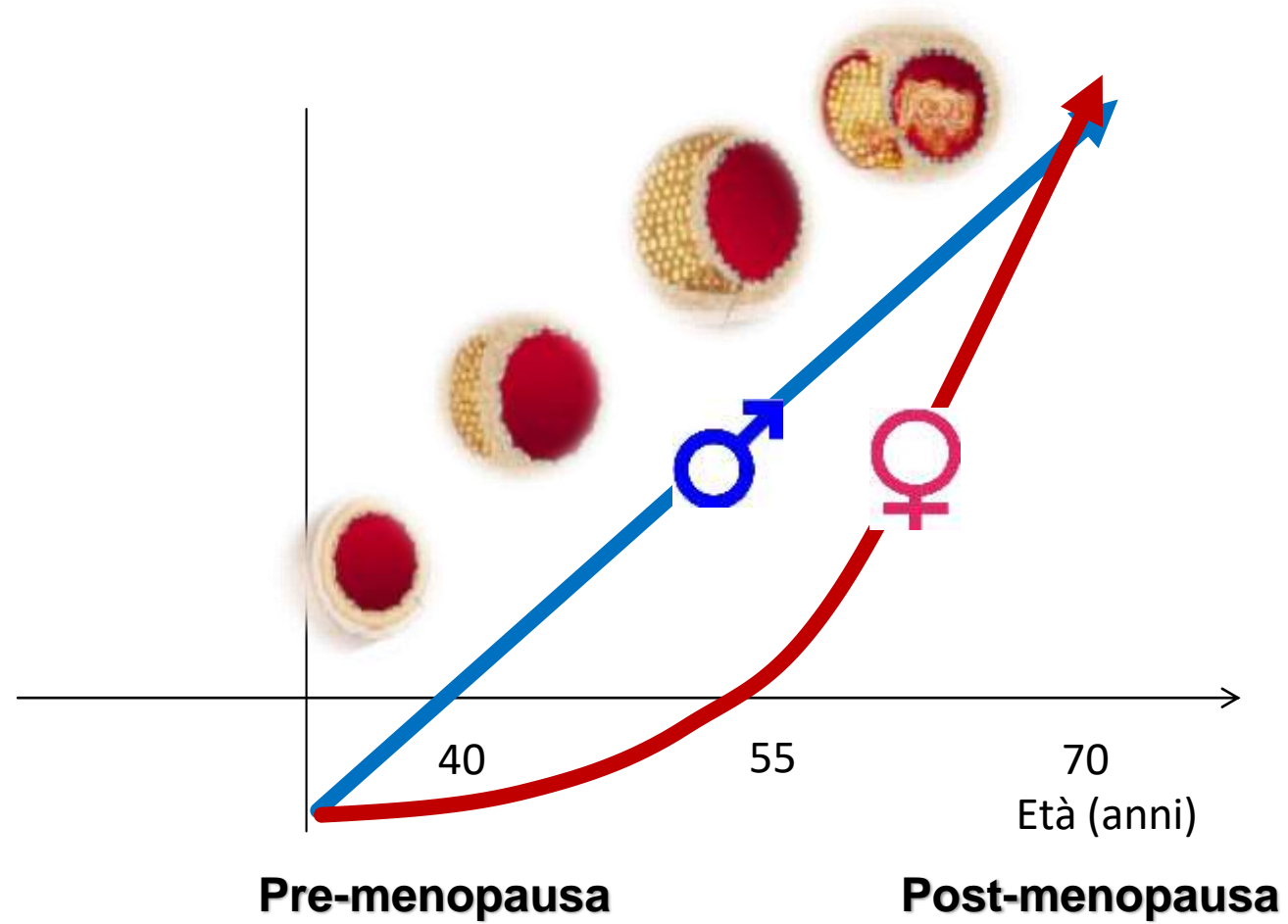


Note: no data available for Andorra.
Source: WHO Mortality Database.

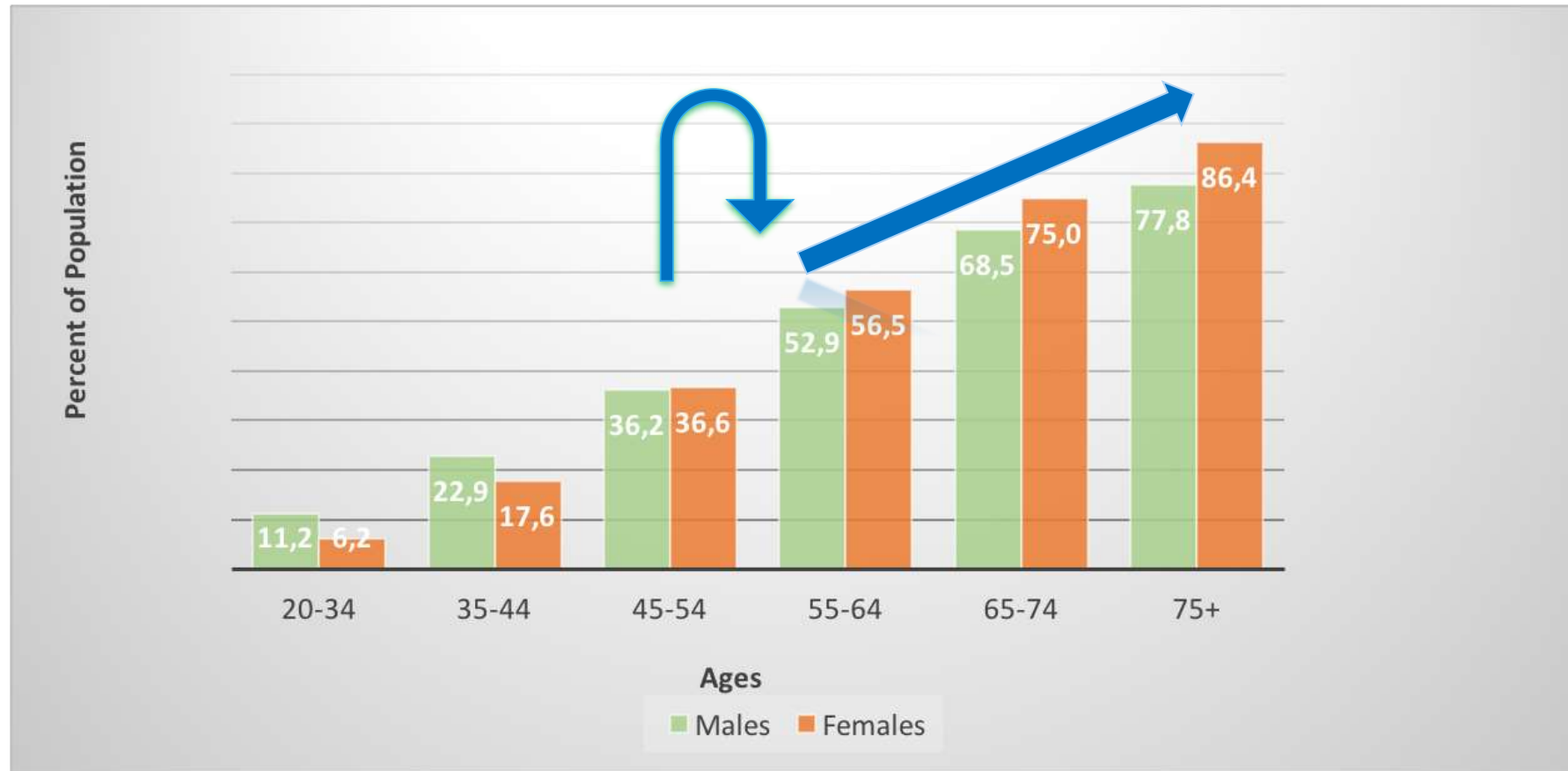
In the EU, CVD is the top cause of death in every European country for women: death from CVD accounted for 43% in women and 36% in men

European Heart Journal (2016) 37, 3232–3245

ETÀ: FATTORE DI RISCHIO PER CORONAROPATIA IN ENTRAMBI I SESSI



PREVALENCE OF CARDIOVASCULAR DISEASES BY AGE AND GENDER



MENOPAUSE AND THE CARDIOVASCULAR RISK IN WOMEN



- The risk for cardiovascular diseases **increases after menopause** because of ovarian hormone deficiency that favours HYPERTENSION, DIABETES, HYPERLIPIDEMIA, CENTRAL OBESITY AND THE METABOLIC SYNDROME.

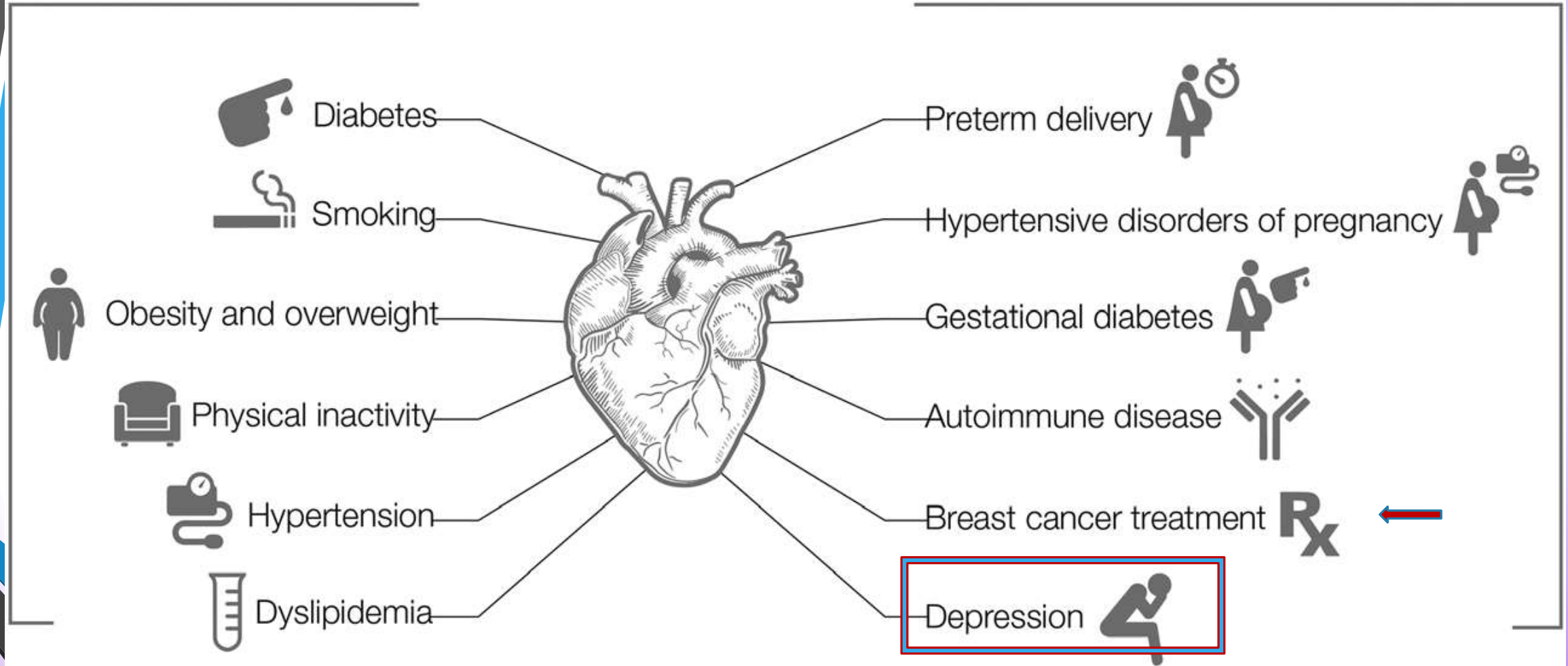


- Menopause may also contribute to the development of **atherosclerosis** by inducing the ENDOTHELIAL DYSFUNCTION.

Traditional and nontraditional atherosclerotic cardiovascular disease (ASCVD) risk factors in women

Traditional ASCVD Risk Factors

Emerging, Nontraditional ASCVD Risk Factors



Women and cardiovascular risk factors

NEW FACTORS

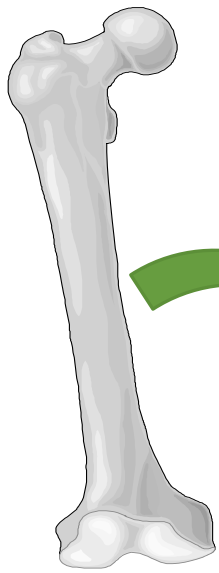
DEPRESSION

- SYSTO-DIASTOLIC HYPERTENSION
- HIGH TOTAL CHOLESTEROL LEVELS
- HIGH LDL-CHOL LEVELS
- OBESITY



- ISOLATED SYSTOLIC HYPERTENSION
- HIGH TRYGLICERIDES LEVELS
- LOW HDL-CHOL LEVELS
- SMOKE
- DIABETES
- METABOLYC SYNDROME
- INFLAMMATORY MARKERS





BONE

Riassorbimento Osseo

Neoformazione Ossea

Assorbimento Calcico

METABOLISM

- Increased sisto-diastolic pression
- Increased Tot-Col and decreased HDL-col
- Increased weight and modified TA distribution
- Insulin resistance

- Osteopenia
- Osteoporosi

MENOPAUSAL CHANGES

Paola Villa

- Hypertension
- Altered Lipid Metabolism
- Obesity
- Glucose Intolerance



How we've changed our thinking about Primary Prevention in Women

RISK FACTORS

- TRIGLYCERIDES, DIABETES, HDL-CHOL
- DEPRESSION
- METABOLIC SYNDROME

Lifestyle Interventions
Preventive Medications
Therapies



NUTRACEUTICAL INTERVENTION??

PHARMA-NUTRITION INTERFACE

Healthy

Prevention of (chronic) Disease

Unhealthy

Diseased

Treatment of (chronic) diseases

Traditional
Diet

Functional
Food

Dietary
supplement

Pharma-
ceutical

Nutrition

Pharma-Nutrition Interface

Pharma

QUALI NUTRACEUTICI ??

FITOESTROGENI E PREVENZIONE

POLYPHENOLIC COMPOUNDS are secondary metabolites produced by plants

Depending on the number of aromatic rings they are divided into the following classes:

- **flavonoids** (most abundant)
- phenolic acids
- stilbene
- Lignans



FLAVONOIDS subclasses:

depends on the degree of oxidation of the pyran ring:
FLAVONOLS, FLAVONES, ISOFLAVONES, FLAVANONES,
anthocyanins, flavanols, catechins, chalcones, aurones, and others .

**Soy and the isoflavones
it contains are gaining
more and more attention
because of the health
benefits associated with
their consumption**



ISOFLAVONI (FITOESTROGENI)

EFFETTI METABOLICI E RISCHIO
CARDIOVASCOLARE



+ Meta-analysis: Results

- ✓ 34/38 trials found soy lowered cholesterol
- ✓ Average of 12.9% decrease in LDL
- ✓ Slight increase in HDL

Anderson et al. NEJM, 1995

- In vitro
 - ✓ inhibit thrombin formation
 - ✓ inhibit platelet activation
- In vivo
 - ✓ modify coagulation responses
 - ✓ affect the progression of atherosclerotic disease

Impact of SOY Proteins on Atherosclerosis

- ✓ Inversely related to initial cholesterol level
- ✓ Considerable individual variation
- ✓ For those with moderately elevated cholesterol, 5 – 10% ↓
- ✓ Effects apparent with 2 – 3 wks

Soy Protein and Cholesterol Reduction

Soy and Cardiovascular health: An overview

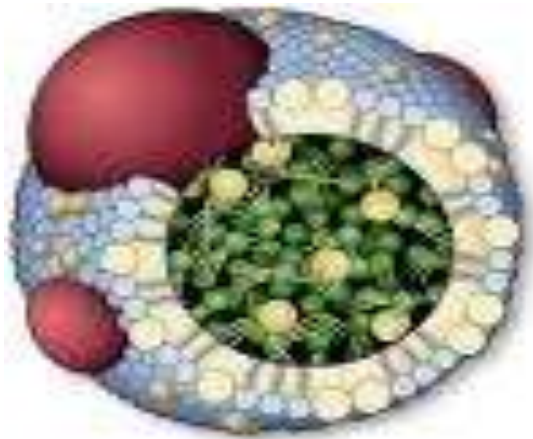
Plasma Lipids and Lipoproteins



AHA Science Advisory

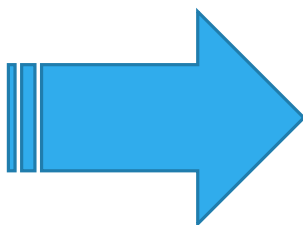
Soy Protein and Cardiovascular Disease
A Statement for Healthcare Professionals From the
Nutrition Committee of the AHA

John W. Erdman, Jr, PhD, for the AHA Nutrition Committee



LDL structure

- Effects of dietary soy protein in human subjects has shown reductions in LDL cholesterol of ~13%, reductions in plasma triglycerides of ~10%, and increases in HDL cholesterol of around 2%
- These beneficial effects of soy protein on plasma lipoproteins culminated recently in the U.S. Food and Drug Administration's approval of the health claim that:
 - “25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease”



Menopause: The Journal of The North American Menopause Society
Vol. 18, No. 7, pp. 732-753
DOI: 10.1097/gme.0b013e31821fc8e0
© 2011 by The North American Menopause Society

NAMS 2011 ISOFLAVONES REPORT

The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010)

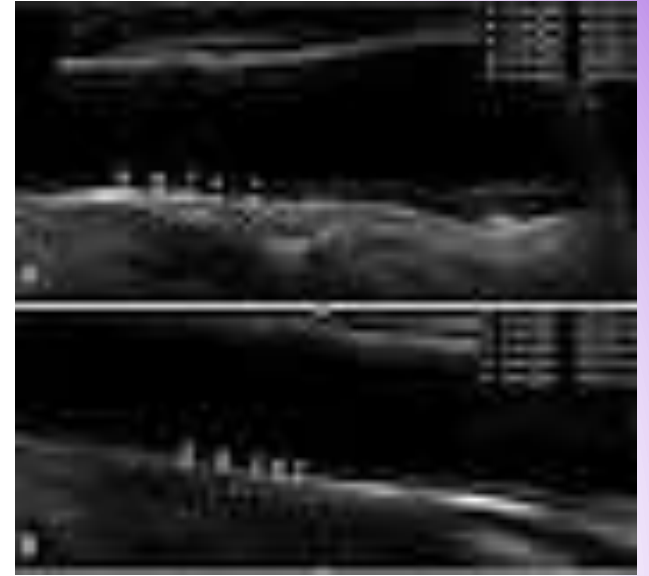
Results: From the hundreds of studies reviewed in this report, there are mixed results of the effects on midlife women. Soy-based isoflavones are modestly effective in relieving menopausal symptoms; supplements providing higher proportions of genistein or increased in S(-)-equol may provide more benefits. Soy food consumption is associated with lower risk of breast and endometrial cancer in observational studies. The efficacy of isoflavones on bone has not been proven, and the clinical picture of whether soy has cardiovascular benefits is still evolving. Preliminary findings on cognitive benefit from isoflavone therapy support a “critical window” hypothesis wherein younger postmenopausal women derive more than older women.

Aglycone	The actual isoflavone without a sugar attached
Daidzein	A diphenolic biochemical, one of three designated as an isoflavone found in high amounts in soy and red clover; the relative amounts of genistein and daidzein are thought to be determinants of therapeutic efficacy of soy supplementation
Equol	A nonsteroidal isoflavone metabolite that is produced from daidzein by intestinal bacteria
Equol nonproducer	A woman or man who cannot convert daidzein to equol
Equol producer	A woman or man who can metabolize daidzein to equol, which enables them to benefit from soy and soy isoflavone products
Estrogen receptors	A group of receptors within cells activated by the hormone 17 β -estradiol and other structurally similar compounds such as isoflavones; generally, the isoflavones have more binding affinity for ER- β than for ER- α
Genistein	A biochemical, one of three designated as an isoflavone found in high amounts in soy and red clover; the relative amounts of genistein and daidzein are thought to be determinants of the therapeutic efficacy of soy supplementation
Glycitein	One of three isoflavones found in soy protein and the protein of other legumes in relatively minor amounts.
Glycoside	A sugar attached to the aglycone portion of an isoflavone
Isoflavone	A plant-derived compound, one of three classes of phytoestrogens, with estrogen-like biologic activity and a chemical structure similar to that of estradiol
Phytoestrogen	Broad term for a plant-derived compound with estrogen-like activity
S(-)-equol	An isomer in the plasma of equol producers and is a metabolite of daidzein
Soy	The most widely used isoflavone-containing food; usually refers to a product derived from the whole soybean
Soy germ	The part of the soybean that has a high concentration of isoflavones, with much more daidzein than genistein and high concentrations of glycitein
Soy isoflavone	Isoflavone derived from soy (as opposed to from red clover)

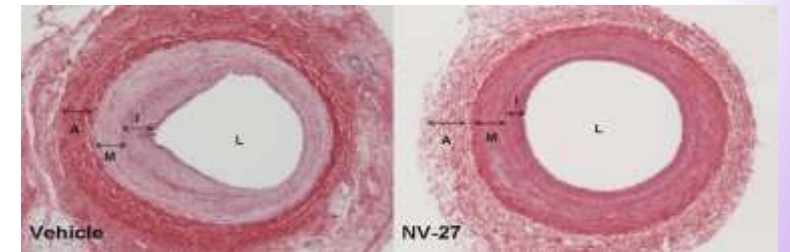
ATHEROSCLEROSIS

Coronary benefits of isoflavones. Isoflavone-rich soy protein was found to reduce the progression of subclinical atherosclerosis as measured by carotid intima media thickness (CIMT).

Hodis et al Stroke 2011

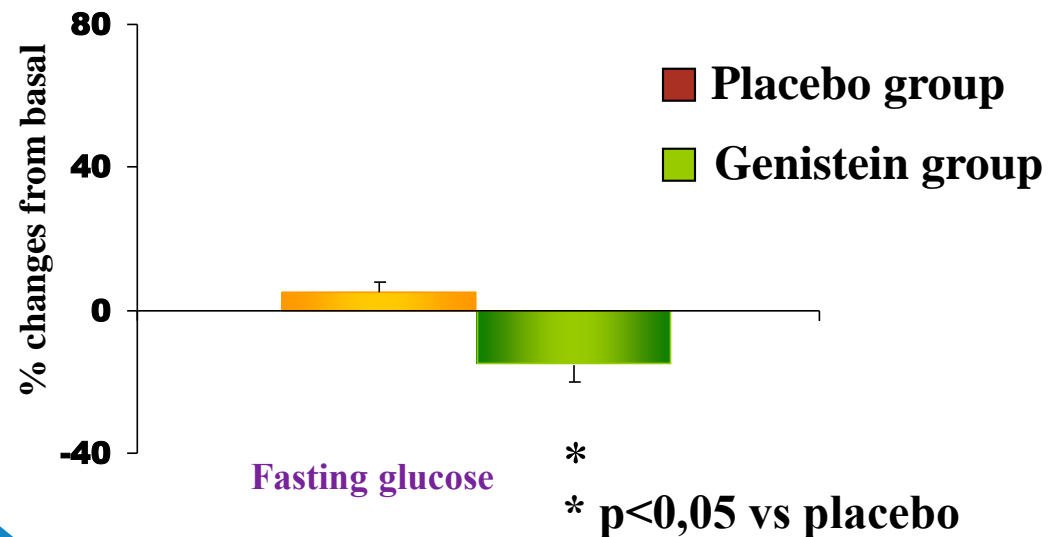
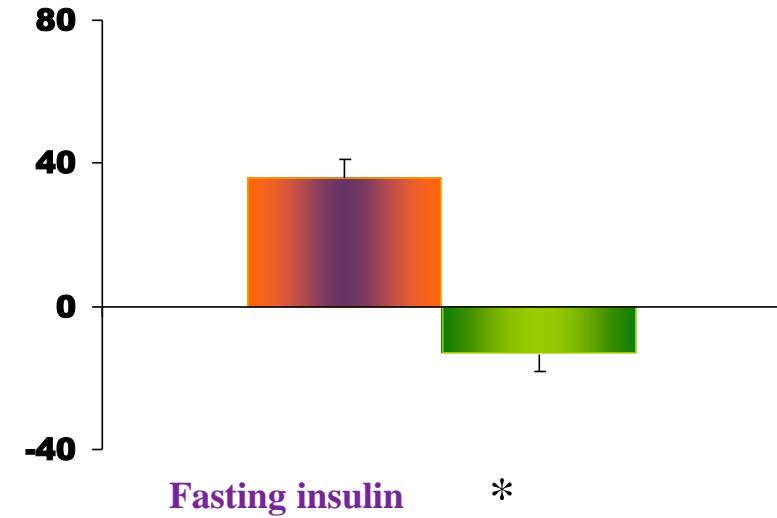
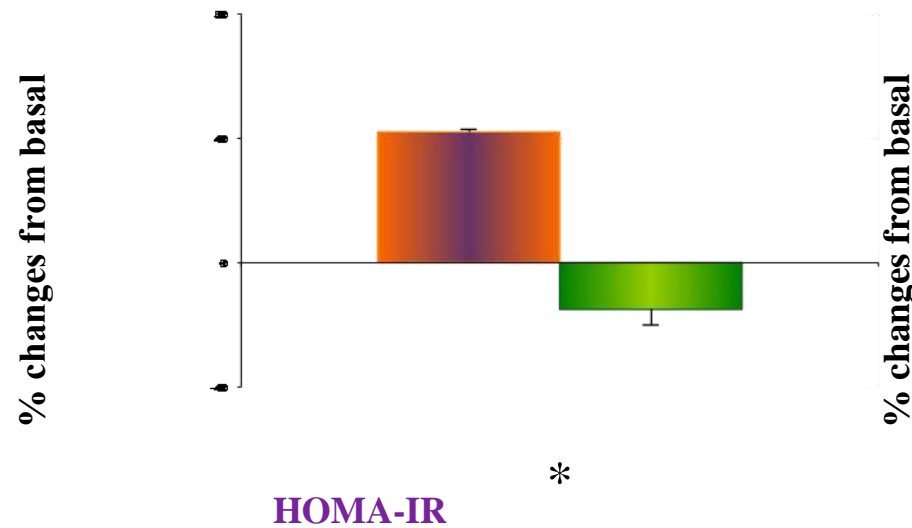


Subanalysis found that among young postmenopausal women (5 y postmenopausal) CIMT progression was reduced by 68% ($P = 0.05$).



Am J Clin Nutr 2014;100(suppl):423S–30S.

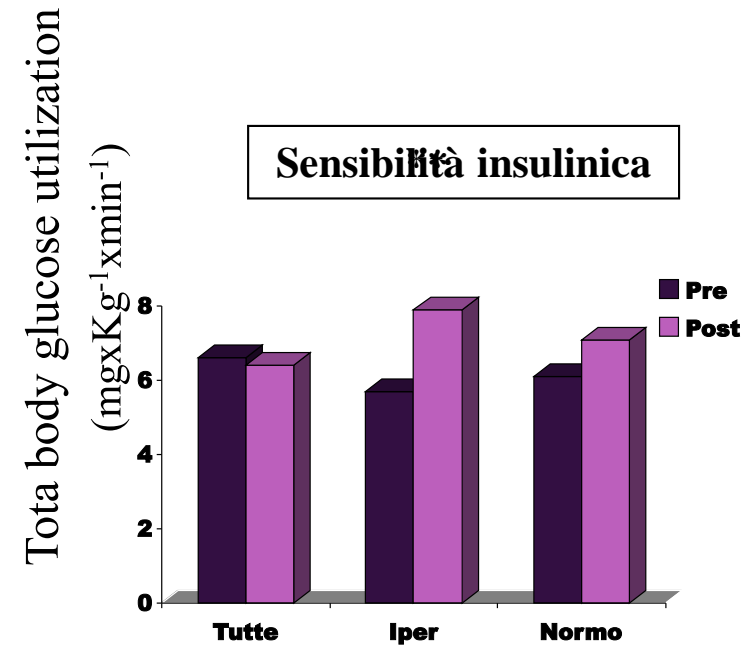
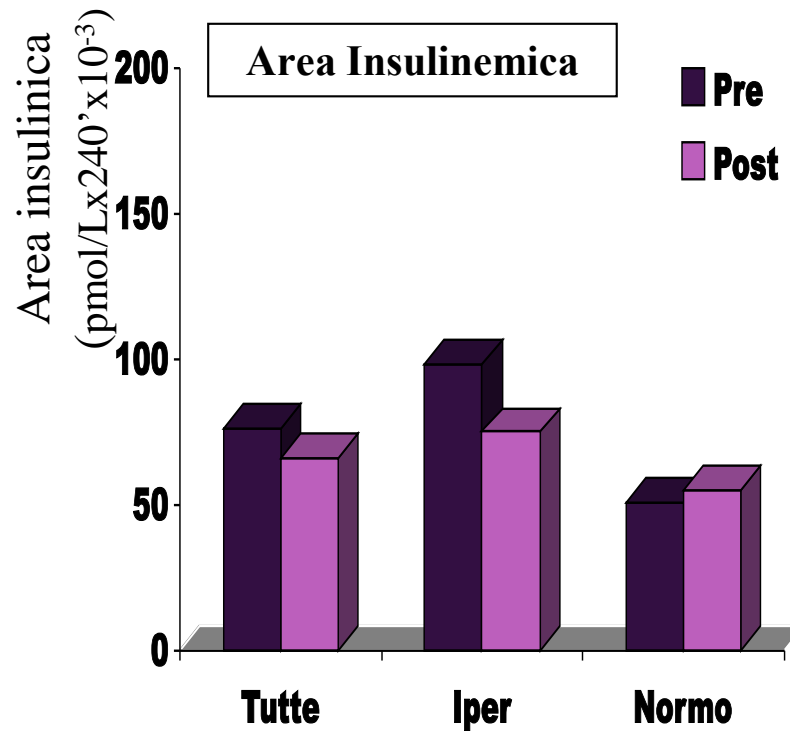
GLUCOSE METABOLISM



Effect of phytoestrogen
genistein on
glyco-insulinemic metabolism
in postmenopausal women

FITOESTROGENI E METABOLISMO GLICO-INSULINEMICO

The differential effect of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women: relationship with the metabolic status.





Review article

The effect of genistein on glucose control and insulin sensitivity in postmenopausal women: A meta-analysis

Yang Liu^{a,b}, Jiapeng Li^{a,b}, Tiansheng Wang^b, Yitong Wang^{a,b}, Libo Zhao^{c,*}, Yi Fang^{a,*}

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^b Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Haidian District, Beijing 100191, China

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2017

Genistein significantly improves glucose control and insulin sensitivity in postmenopausal women.

Long-term treatment may have greater effects than short-term use.

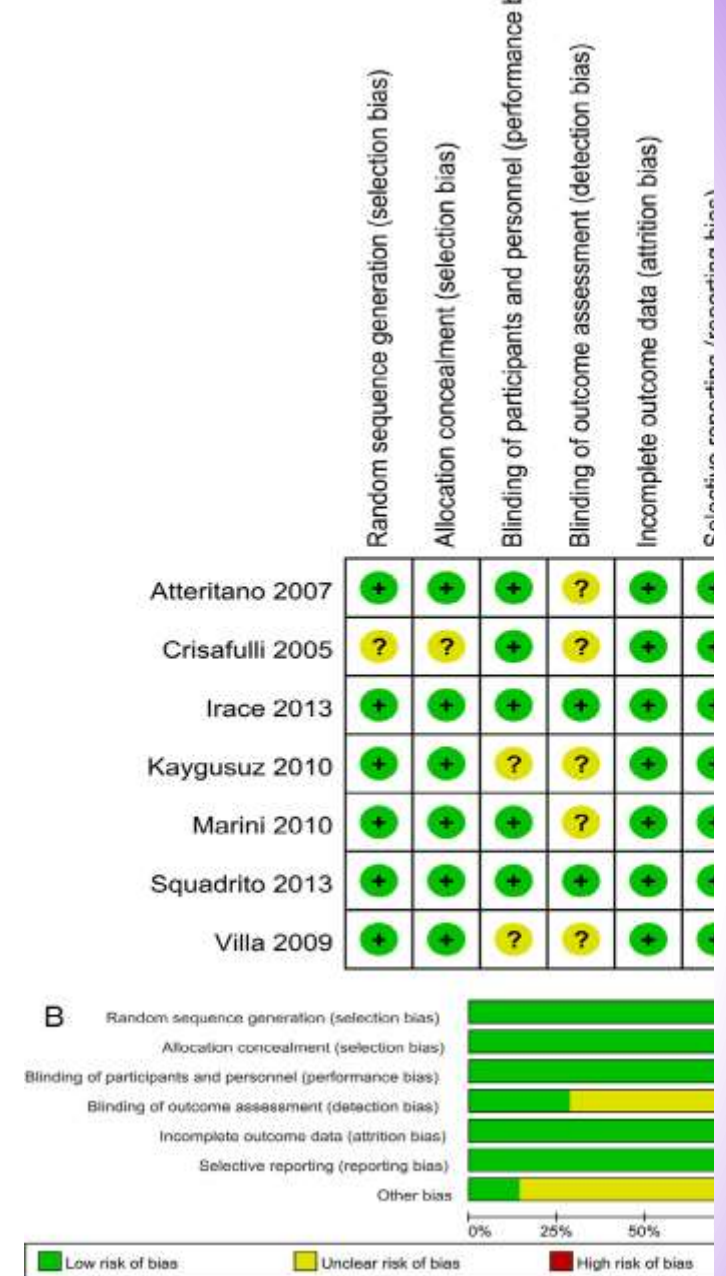
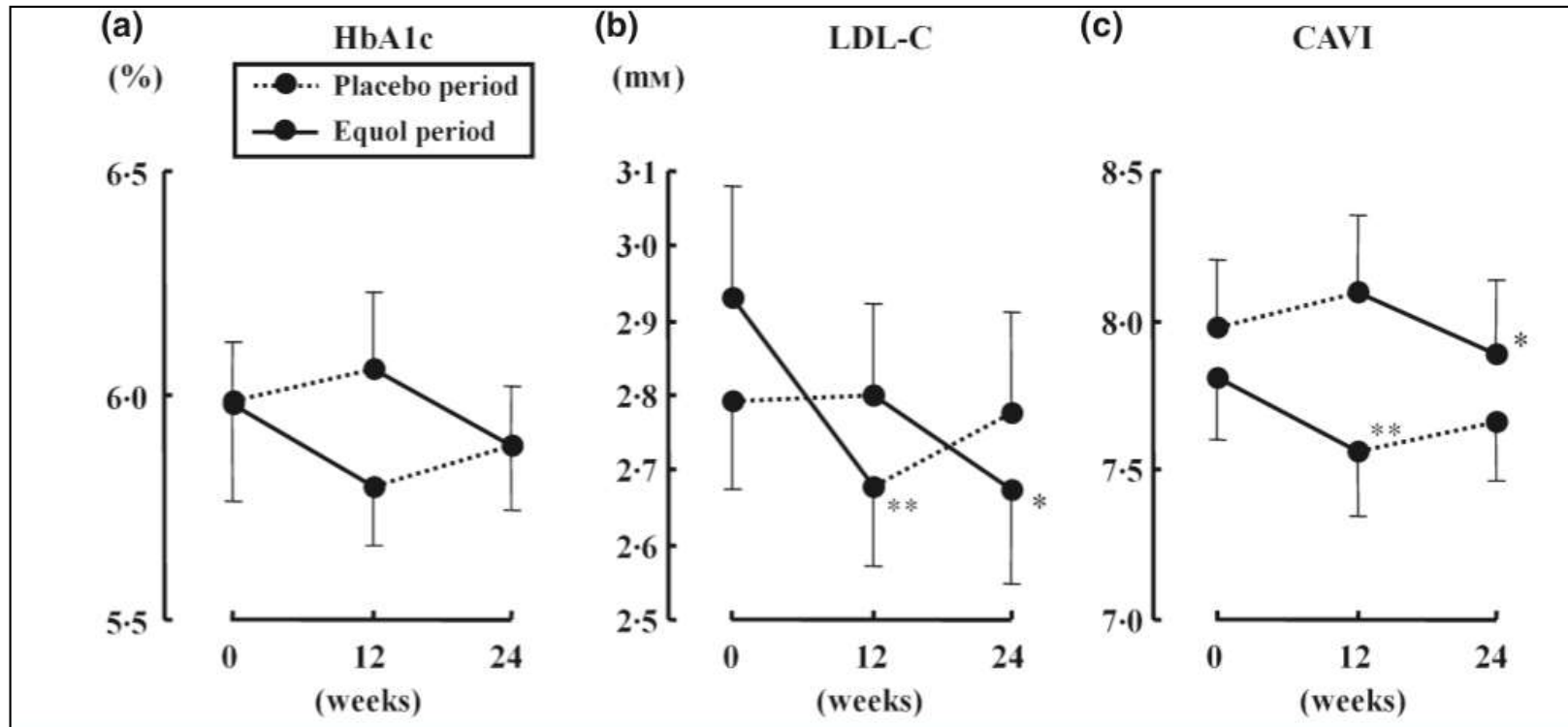
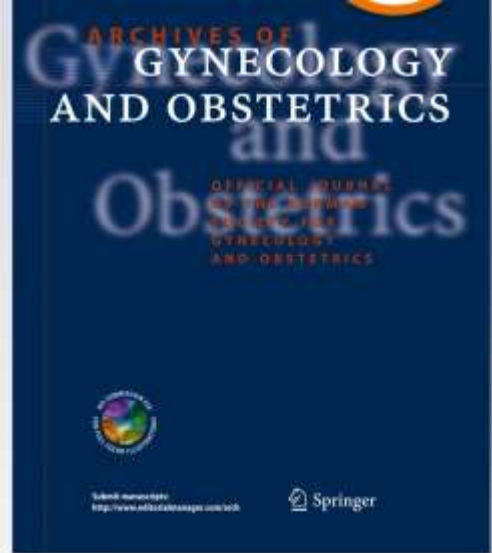


Fig. 2. (A) Risk of bias summary: review authors' judgments about each of bias for each included study. +low risk of bias; -high risk of bias; ? unclear risk of bias. (B) Risk of bias graph: review authors' judgments about each item's risk of bias presented as percentage across all included studies.



Compared with the placebo group, intervention with natural S-equol led to a significant decrease in HbA1c, serum low-density lipoprotein cholesterol (LDL-C) levels and CAVI score.



The impact of combined nutraceutical supplementation on quality of life and metabolic changes during the menopausal transition: a pilot randomized trial

Paola Villa¹ · Inbal D. Amar¹ · Carolina Bottoni¹ · Clelia Cipolla¹ · Giorgia Dinoi¹ · Maria C. Moruzzi¹ · Giovanni Scambia¹ · Antonio Lanzone¹

2017

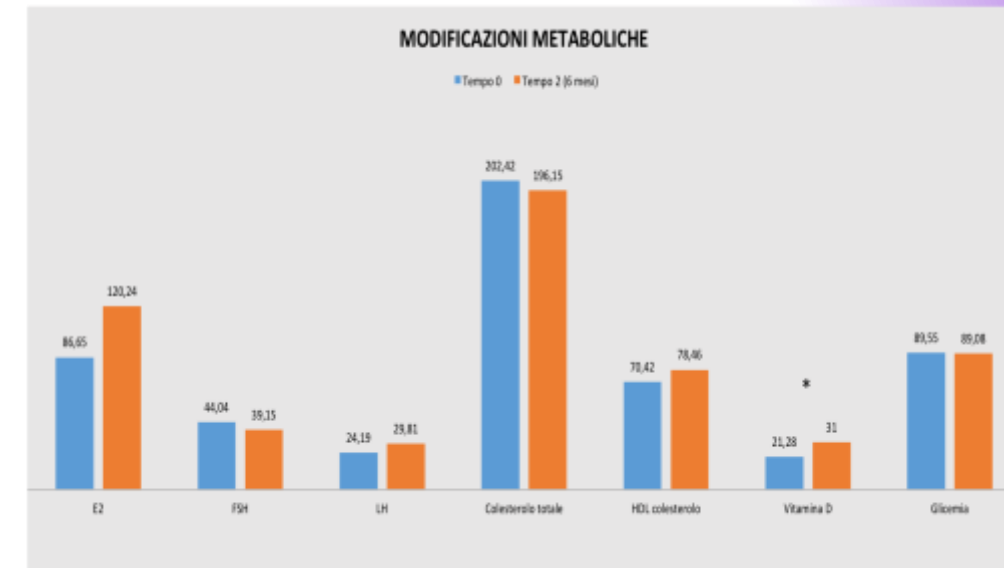
Table 2 Endocrine and metabolic changes before and after 6 months of nutraceutical supplementation in the study group and in controls

	Study group			Controls		
	Baseline	6 months	<i>p</i>	Baseline	6 months	<i>p</i>
BMI, kg/m ²	23.1 ± 3.9	22.5 ± 2.8		23.5 ± 2.6	24 ± 1.9	
E2, pg/mL	69.1 ± 77.3	75.8 ± 87.7		72.4 ± 46.1	68.8 ± 87.7	
FSH, mUI/mL	48.5 ± 27.9	50.0 ± 28.9		45.4 ± 29.0	50.0 ± 28.9	
LH, mUI/mL	25.7 ± 14.6	30.3 ± 20.4		22.1 ± 13.3	29.5 ± 23.8	
Total cholesterol, mg/dL	208.2 ± 33.7	198.2 ± 27.2		194.7 ± 18.7	212.1 ± 27.1	0.05
LDL cholesterol, mg/dL	122.0 ± 32.0	120.7 ± 25.1		121.8 ± 17.6	114.5 ± 30.1	
HDL cholesterol, mg/dL	64.9 ± 15.0	67.1 ± 12.5*		60.5 ± 11.1	58.1 ± 13.3	
Triglycerides, mg/dL	91.4 ± 30.0	88.0 ± 39.6		92.7 ± 33.1	92.2 ± 43.7	
Glucose mg/mL	88.7 ± 6.2	87.3 ± 5.7		88.9 ± 10.2	89.5 ± 8.5	
Insulin, µUI/mL	8.6 ± 2.5	8.4 ± 2.5		8.9 ± 2.7	9.1 ± 3.3	
Vitamin D, ng/mL	22.6 ± 8.0	30.4 ± 8.8	0.01	19.3 ± 5.0	22.7 ± 4.7	

BMI body mass index, E2 estradiol, FSH follicle-stimulating hormone, HDL high-density lipoprotein, LDL low-density lipoprotein, LH luteinizing hormone

* *p* < 0.05 for patients vs controls at 6 months

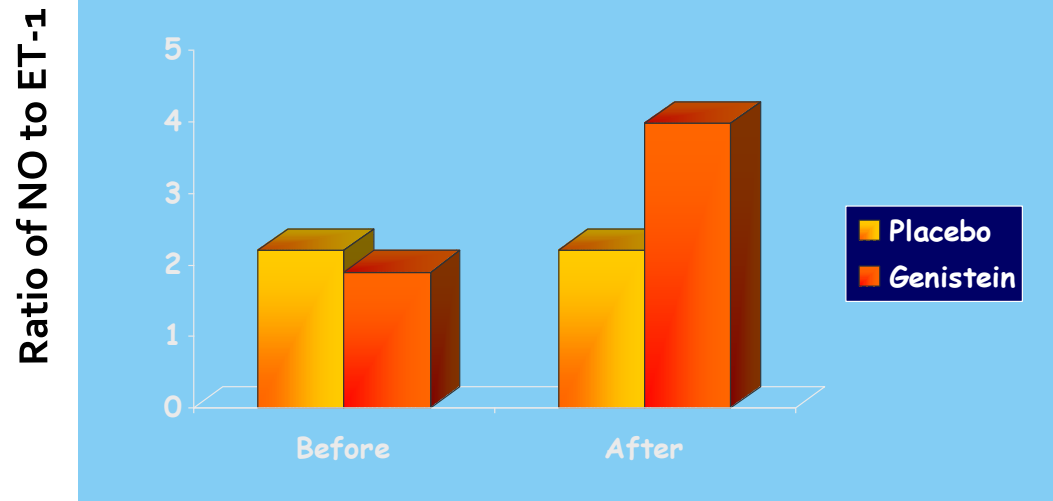
EQUOLO E METABOLISMO LIPIDICO



STABILIZZAZIONE DELLE
MODIFICAZIONI METABOLICHE in
PERIMENOPAUSA
MIGLIORAMENTO SIGNIFICATIVO
di HDL

GENISTEINA E ENDOTELIO

Ratio of NO to ET-1



The differential effect of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women: relationship with the metabolic status.

Villa P et al. J Clin Endocrinol Metab. 2009 Feb; 84(2)

Absolute change in brachial artery diameter

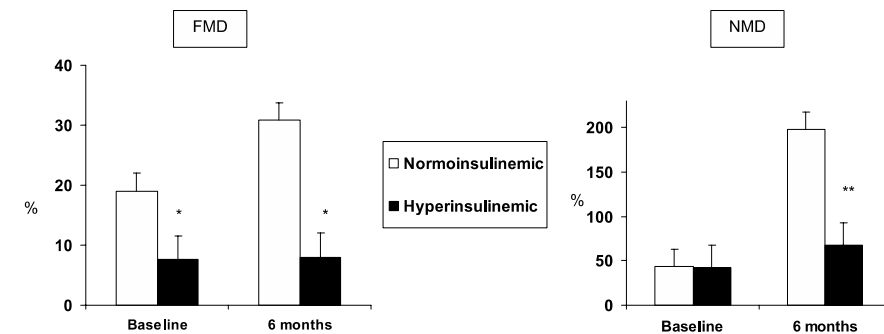
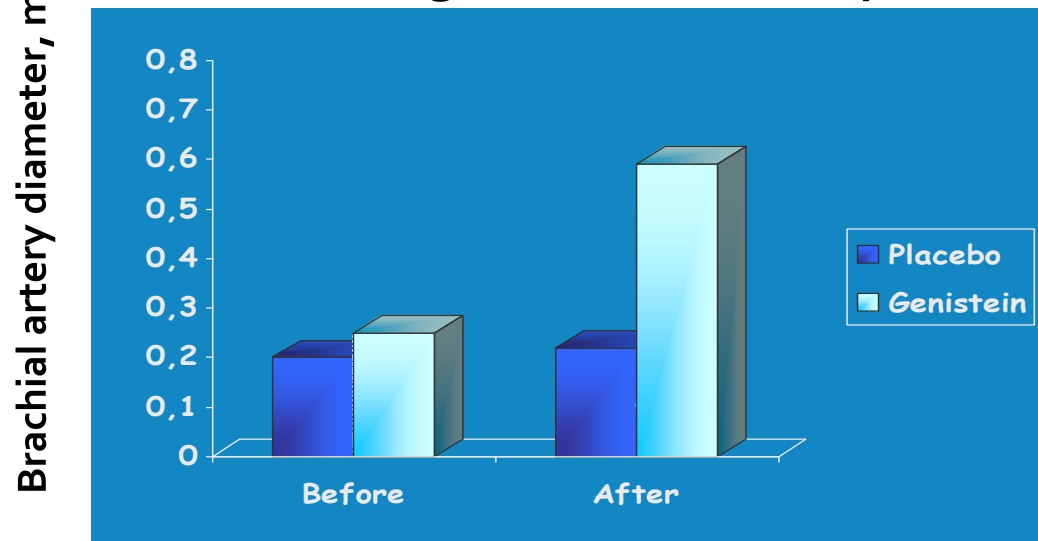
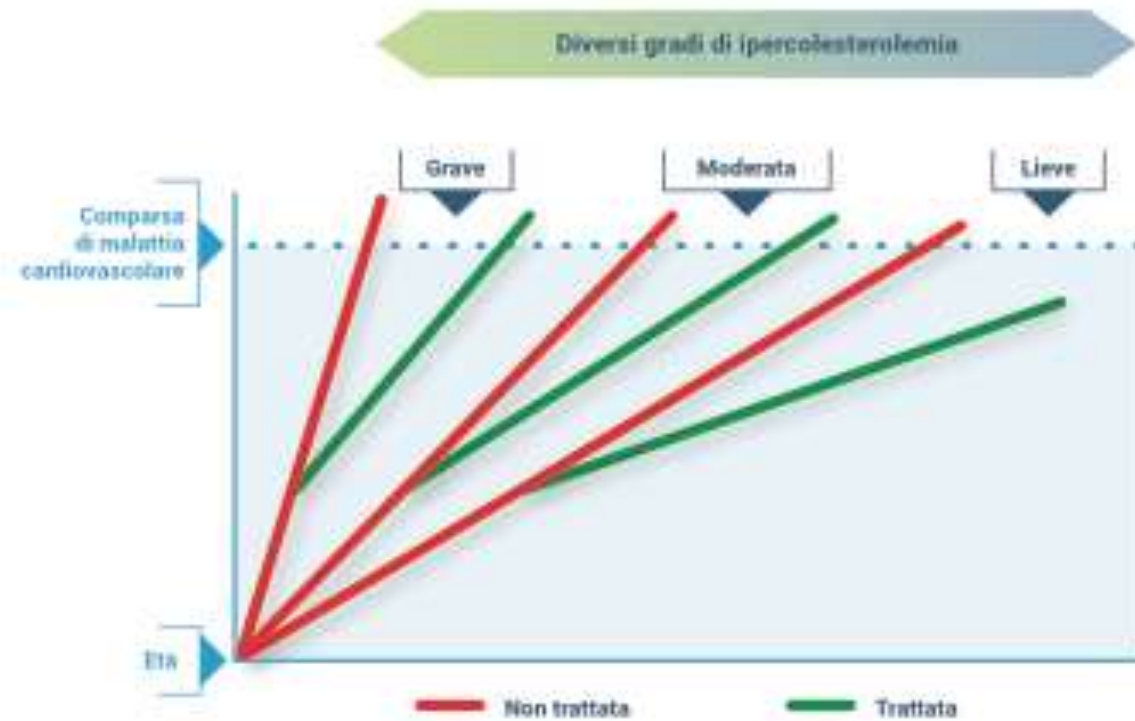


FIG. 1. Brachial artery flow evaluation: percent increase after FMD and NMD at baseline and after the 24-wk therapy. Black bars, Hyperinsulinemic patients; white bars, normoinsulinemic patients. Significance for pretreatment vs. posttreatment values of FMD and NMD in normoinsulinemic women is as follows: $P < 0.02$ and $P < 0.001$, respectively. *, $P < 0.001$, normoinsulinemic vs. hyperinsulinemic; **, $P < 0.01$, normoinsulinemic vs. hyperinsulinemic.

Squadrito et al. Atherosclerosis 2002

RISCHIO C ARDIOVASCOLARE E IPERLIPIDEMIA

A valori più bassi della colesterolemia LDL corrisponde, costantemente, un minore rischio cardiovascolare (“the lower, the better”)



Livelli anche solo moderatamente elevati dei fattori di rischio cardiovascolare possono con maggiore probabilità – a causa della maggiore durata dell’esposizione – indurre la comparsa di eventi clinici.

La Monacolina K : Riso rosso fermentato

- ❖ Il riso rosso fermentato è ottenuto dalla fermentazione del comune riso da cucina (*Oryza sativa*), ad opera di un particolare lievito, chiamato *Monascus purpureus* o lievito rosso, costituito da pigmenti in genere di colore rosso e un gruppo di molecole ad attività inibitoria sulla sintesi epatica del colesterolo (monacoline) tra cui la più efficace è la MONACOLINA K
- ❖ la monacolina K è in grado di inibire con buona efficacia l'enzima limitante nella sintesi del colesterolo, l'HMG-CoA Reduttasi.



La Gazzetta Ufficiale dell'Unione Europea datata Maggio 2012

Sostanza nutritiva, sostanza di altro tipo, alimento o categoria di alimenti	Indicazione	Condizioni d'uso dell'indicazione	Condizioni e/o restrizioni d'uso dell'alimento e/o dicitura o avvertenza supplementare	Numero dell'EFSA Journal	Numero delle pertinenti voci nell'elenco consolidato sottoposto alla valutazione dell'EFSA
Monascus purpureus (riso rosso)	La monacolina K del riso rosso contribuisce al mantenimento di livelli normali di colesterolo nel sangue	Questa indicazione può essere impiegata solo per un alimento che fornisce un apporto giornaliero di 10 mg di monacolina K del riso rosso. L'indicazione va accompagnata dall'informazione al consumatore che l'effetto benefico si ottiene con l'assunzione giornaliera di 10 mg di monacolina K da preparazioni di riso rosso fermentato.		2011;9(7):2304	1648, 1700

25.5.2012
IT

Monacolina K

Dopo attenta valutazione e revisione degli studi clinici riconosce questa indicazione: la Monacolina K contribuisce al mantenimento di livelli normali di colesterolo nel sangue.

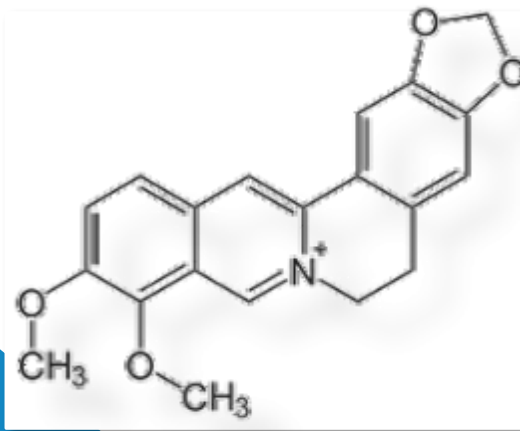
metabolizzata dal citocromo P₄₅₀, dall'isoenzima 3A₄, che interviene nel metabolismo di quasi il 30% dei farmaci.

Non è raccomandata la combinazione di statine con integratori a base di riso rosso fermentato, sia per motivi farmacodinamici (il meccanismo d'azione è lo stesso sia per la possibilità di indurre gli stessi effetti collaterali).

Berberina

La **berberina** è un alcaloide isochinolinico vegetale appartenente alla classe delle protoberberine presenti in diverse piante (radici, rizomi, gambi, frutti e corteccia) quali *Coptis* (*Coptis chinensis* e *japonica*), *Hydrastis* (*Hydrastis canadensis*) e *Berberis* (*Berberis aristata*, *vulgaris* e *croatica*).

isoquinoline alkaloids



Pirro M et al, *Nutr Metab Cardiovasc Dis* 2017;27:2-17
Rivellese AA & Pirro M, *Giorn Ital Arterioscler* 2016;7(2):3-29
Hunter PM & Hegele RA, *Nat Rev Endocrinol* 2017;13:278-289
Cicero AFG et al, *Arch Med Sci* 2017;13,5:965-1005
Cicero AFG et al, *Nutr Rev* 2017;75(9):731-767



Berberina

Si è dimostrata efficace nel controllo del colesterolo legato alle lipoproteine LDL, ma anche nell'influenzare favorevolmente il profilo lipidemico complessivo (inclusi quindi i livelli plasmatici dei trigliceridi e del colesterolo HDL) e la glicemia

Riduce i livelli plasmatici di una proteina PCSK9 e stabilizza i livelli di RNAm che codifica per il rec LDL determinando una maggiore presenza di recettori per LDL sulla superficie delle cc epatiche facilitando la captazione delle LDL e riducendone i livelli plasmatici

METABOLISMO LIPIDICO

Il meccanismo di controllo della glicemia da parte della berberina è pure complesso, e correla sia con la capacità di questa molecola di ridurre l'assorbimento intestinale di glucosio e sia con l'effetto di aumento della captazione muscolare ed epatica del glucosio stesso. La molecola svolgerebbe infatti un'azione di tipo incretinico (aumentando il rilascio di GLP-1, e quindi di insulina) ma anche di sensibilizzazione all'insulina

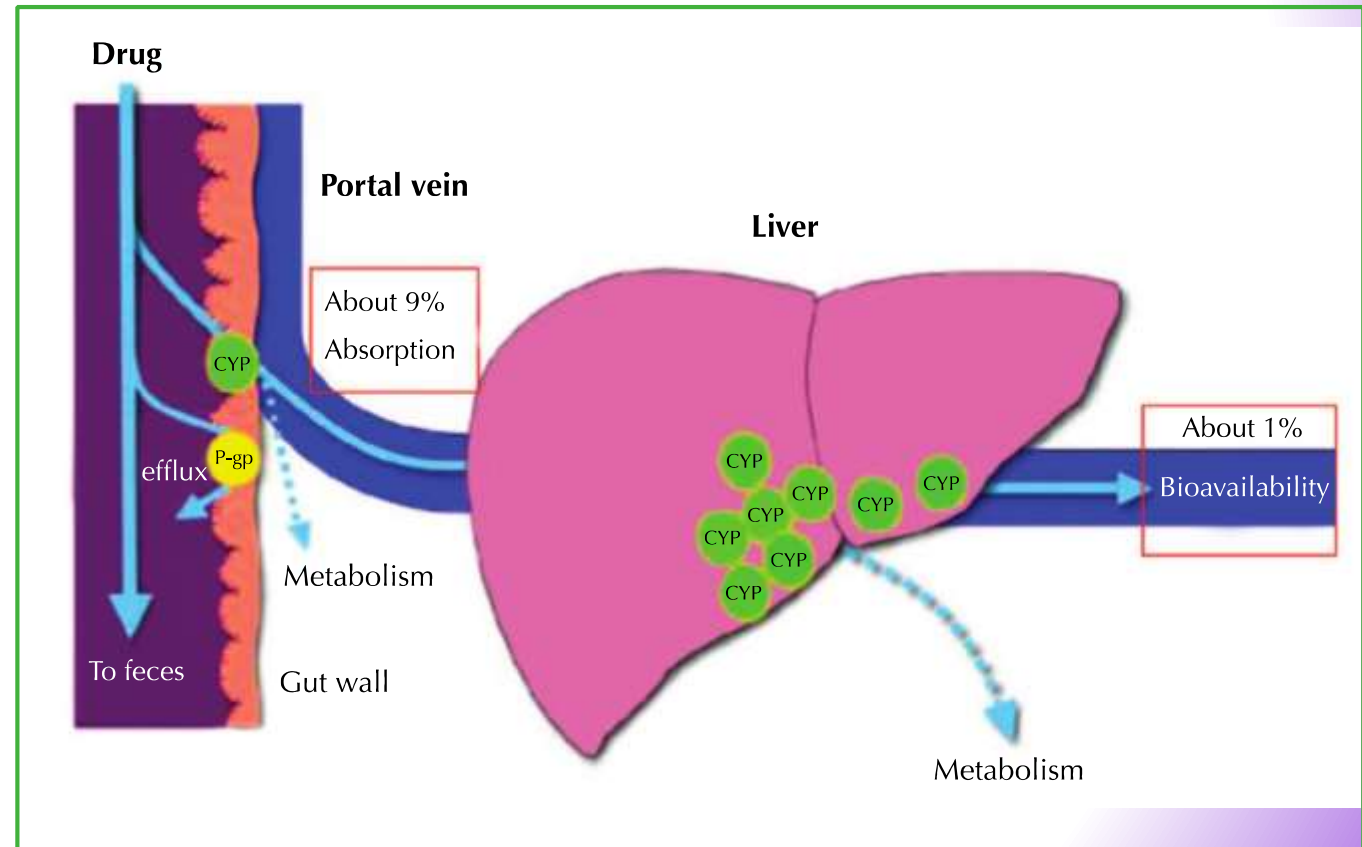
METABOLISMO GLUCIDICO

BERBERINA : FARMACOCINETICA

La biodisponibilità molto bassa (2-3%) può condurre a significative differenze nella risposta metabolica alla sua assunzione.

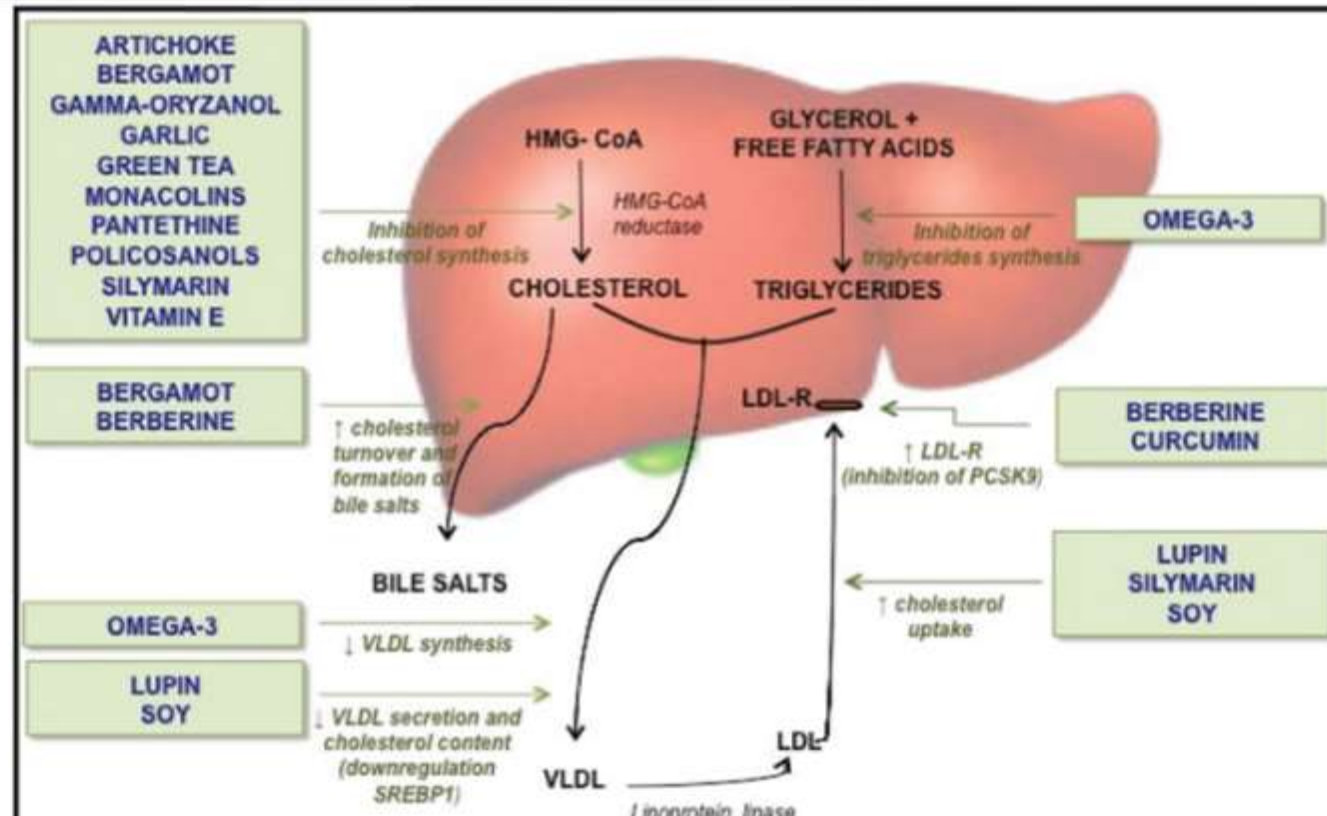
Sono attualmente allo studio interventi di varia natura finalizzati ad aumentarne l'assorbimento intestinale

ASSORBIMENTO INTESTINALE



2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)



5.5.5. Policosanol and berberine

Policosanol is a natural mixture of long chain aliphatic alcohols extracted primarily from sugarcane wax.¹⁸⁸ Studies show that poli-
cosanol from sugarcane, rice or wheat germ has no significant effect
on LDL-C, HDL-C, TGs, apoB, Lp(a), homocysteine, hs-CRP, fibrin-
ogen or blood coagulation factors.¹⁸⁹

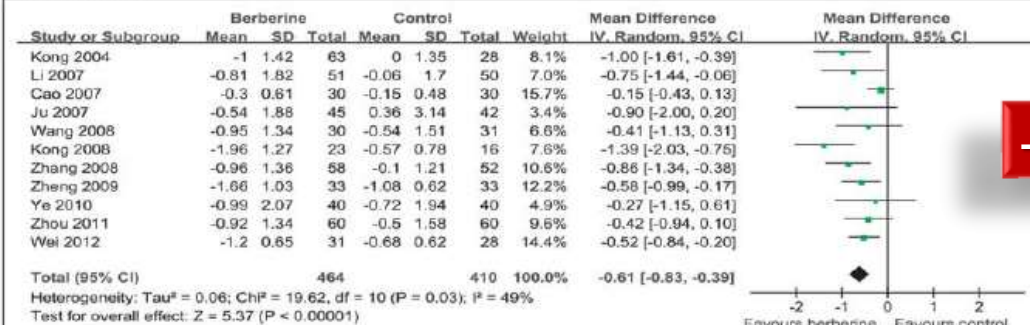
As for berberine, a recent meta-analysis has evaluated its ef-
fects on plasma lipids in humans; six trials were available for
this purpose: the berberine group contained 229 patients and
the control group contained 222 patients.¹⁹⁰ The studies,
showing a statistically significant heterogeneity, were all per-
formed in China in people of Asian ethnicity. The comparative
evaluation of berberine and lifestyle intervention or placebo indi-
cated that in the berberine group, LDL-C and plasma TG levels
were more effectively reduced than in the control group. Howev-
er, due to the lack of high-quality randomized clinical trials, the
efficacy of berberine for treating dyslipidaemia needs to be
further validated.

The Effects of Berberine on Blood Lipids: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

Dong H et al. The Effects of... Planta Med 2013; 79: 437-446

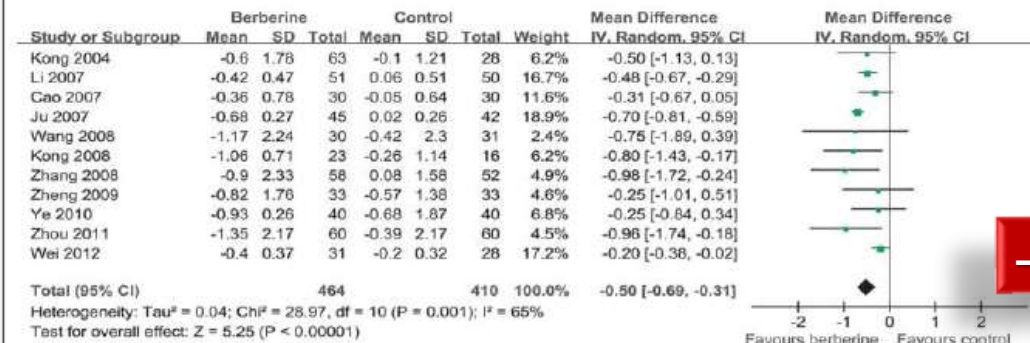
11 TRIALS CLINICI

TC (mmol/L)



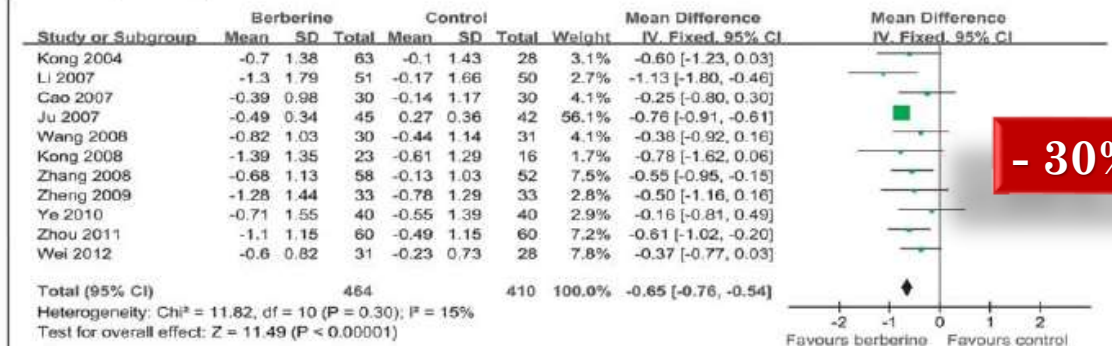
- 25%

TG (mmol/L)



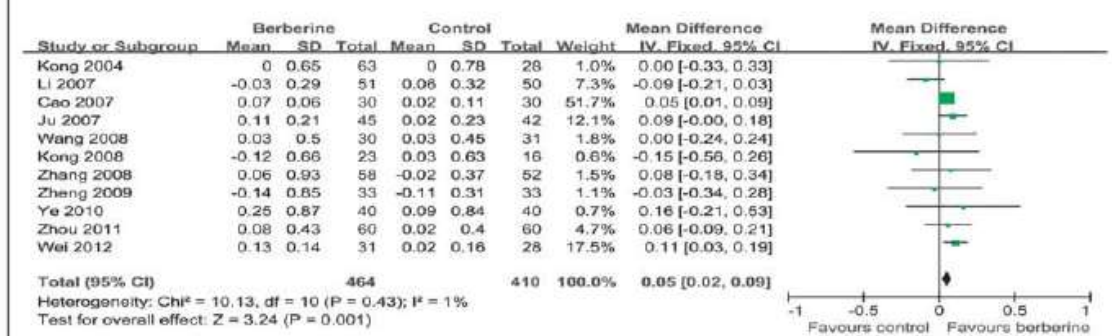
- 20%

LDL-C (mmol/L)



- 30%

HDL-C (mmol/L)

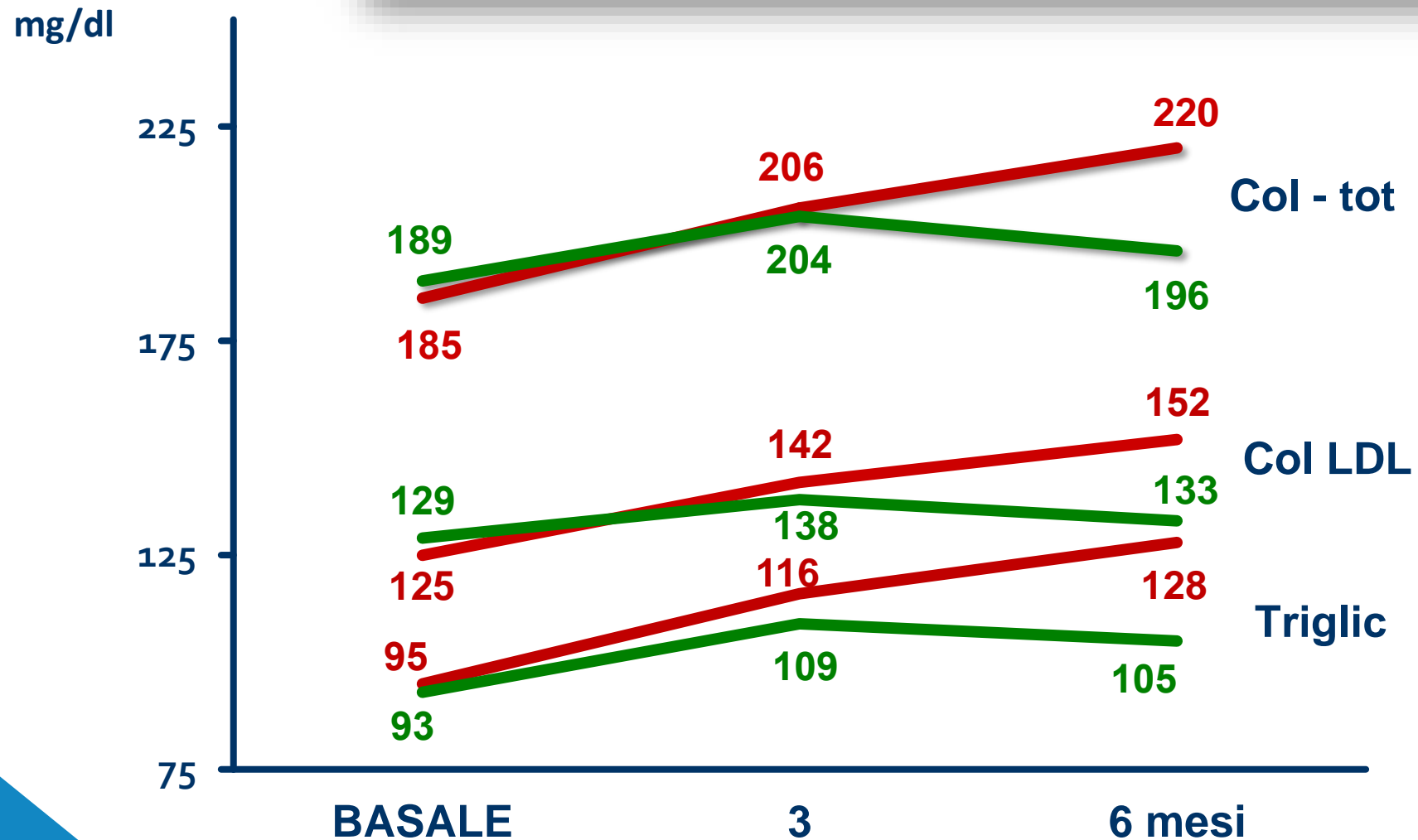


137 soggetti
statina ½ dose +

— placebo vs

— berberina 1000 mg/die

Berberis aristata combined with *Silybum marianum* on lipid profile in patients not tolerating statins at high doses



NUTRACEUTICI, INTEGRATORI E ALIMENTI FUNZIONALI NEL CONTROLLO DELLA COLESTEROLEMIA

UNA GUIDA PER IL MEDICO

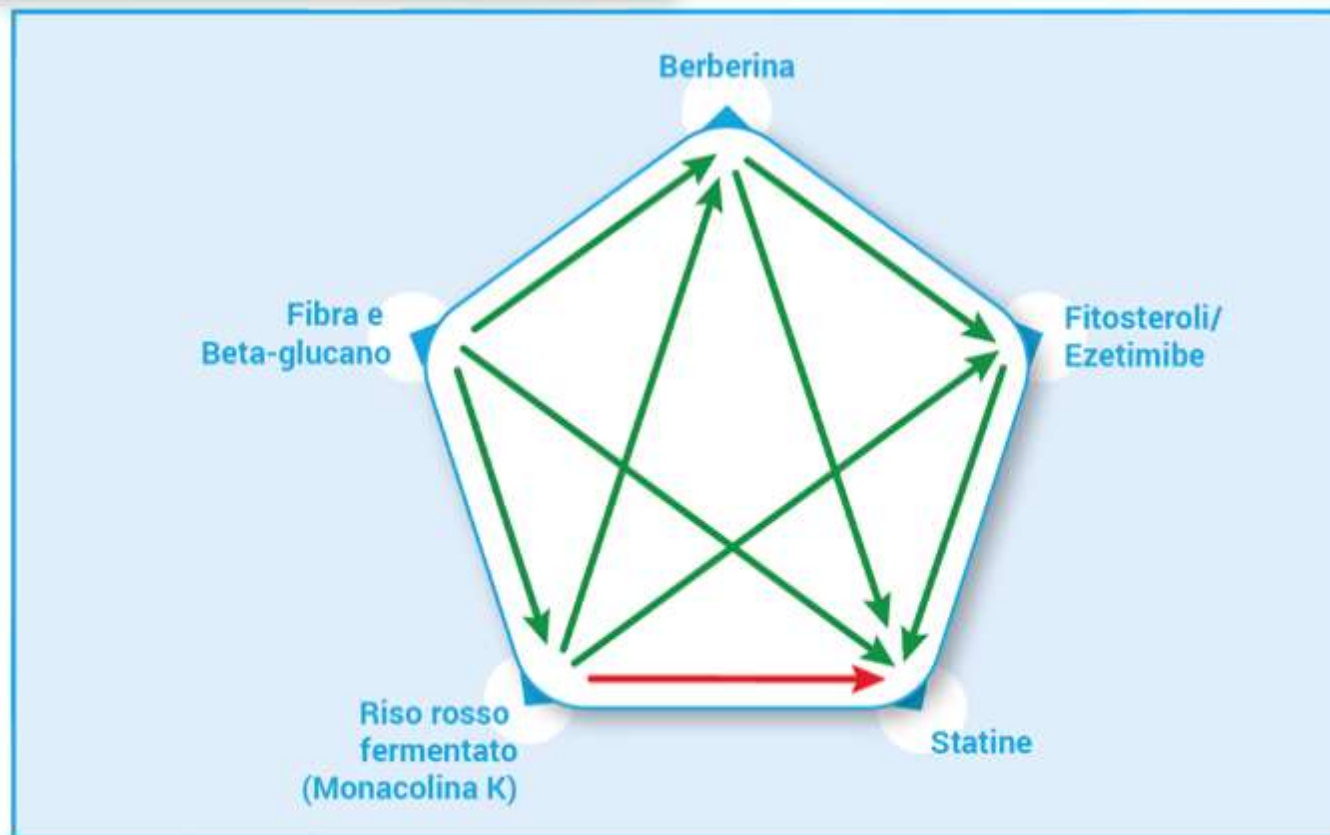


Figura 3

Possibili combinazioni di principi ad azione ipocolesterolemizzante.

Frecce verdi: combinazioni razionali. Frecce rosse: combinazioni non raccomandate

NUTRACEUTICI, INTEGRATORI E ALIMENTI FUNZIONALI NEL CONTROLLO DELLA COLESTEROLEMIA

UNA GUIDA PER IL MEDICO

Tabella 2

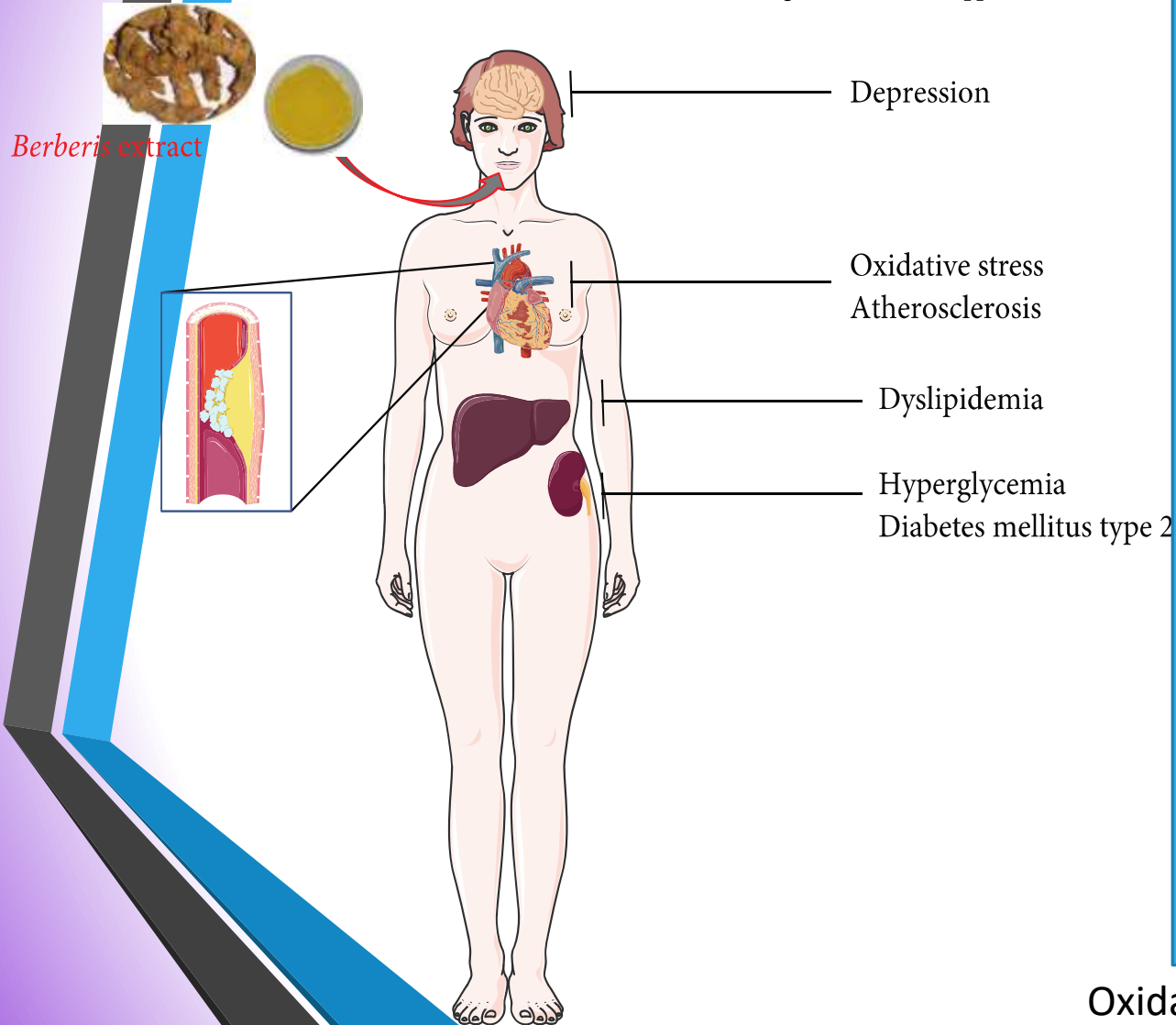
Effetto sulla colesterolemia LDL di alcuni dei principi esaminati nei capitoli precedenti (dato medio rilevato o ricalcolato dalle meta-analisi citate).

Principio Attivo	Dose	Effetto sulla colesterolemia LDL
Steroli e stanoli vegetali	1,5-3,0 g/die	-9,1-18,2 mg/dL ²⁶
Riso rosso fermentato	3-10 mg/die (titolato in Monacolina K)	-33,4 mg/dL (-27,3-39,6 mg/dL) ³³
Beta-glucano	3,4 g/die	-7,3 mg/dL (-5,4-8,8 mg/dL) ⁴⁴
Policosanoli	10-80 mg/die	0,0 mg/dL (-13,8 -13,8 mg/dL) ⁶⁰
Berberina	500-1500 mg/die	-25,0 mg/dL (-20,7-29,2 mg/dL) ⁴⁵
Proteine della soia	25-50 g/die	-4,8 mg/dL (-2,3-7,3 mg/dL) ⁵²

Review Article

Potential Benefits of Berberine in the Management of Perimenopausal Syndrome

Cristiana Caliceti,¹ Paola Rizzo,^{1,2} and Arrigo Francesco Giuseppe Cicero³



PAZIENTE IN PERIMENOPAUSA FASE DI TRANSIZIONE E FASE INIZIALE

Indicazioni per

- menopause-associated pathologies (oxidative stress, inflammation and hypercholesterolemia-related cardiovascular diseases, hyperglycemia-related diabetes mellitus type 2, and depression)
- improvement of quality of life in menopausal women.

PREVENZIONE DEL RISCHIO CARDIOVASCOLARE

Strategie di prevenzione cardiovascolare

Approccio classico



Approccio ragionato

