

14° CONGRESSO NAZIONALE SINut

SINut
Società Italiana di Nutraceutica

12-14 settembre 2024
Bologna



**Dalla complessità del
metabolismo lipidico
all'approccio multitarget:
una proposta operativa**
Arrigo F.G. Cicero

Dip. di Scienze Mediche e Chirurgiche
Alma Mater Studiorum Università di
Bologna

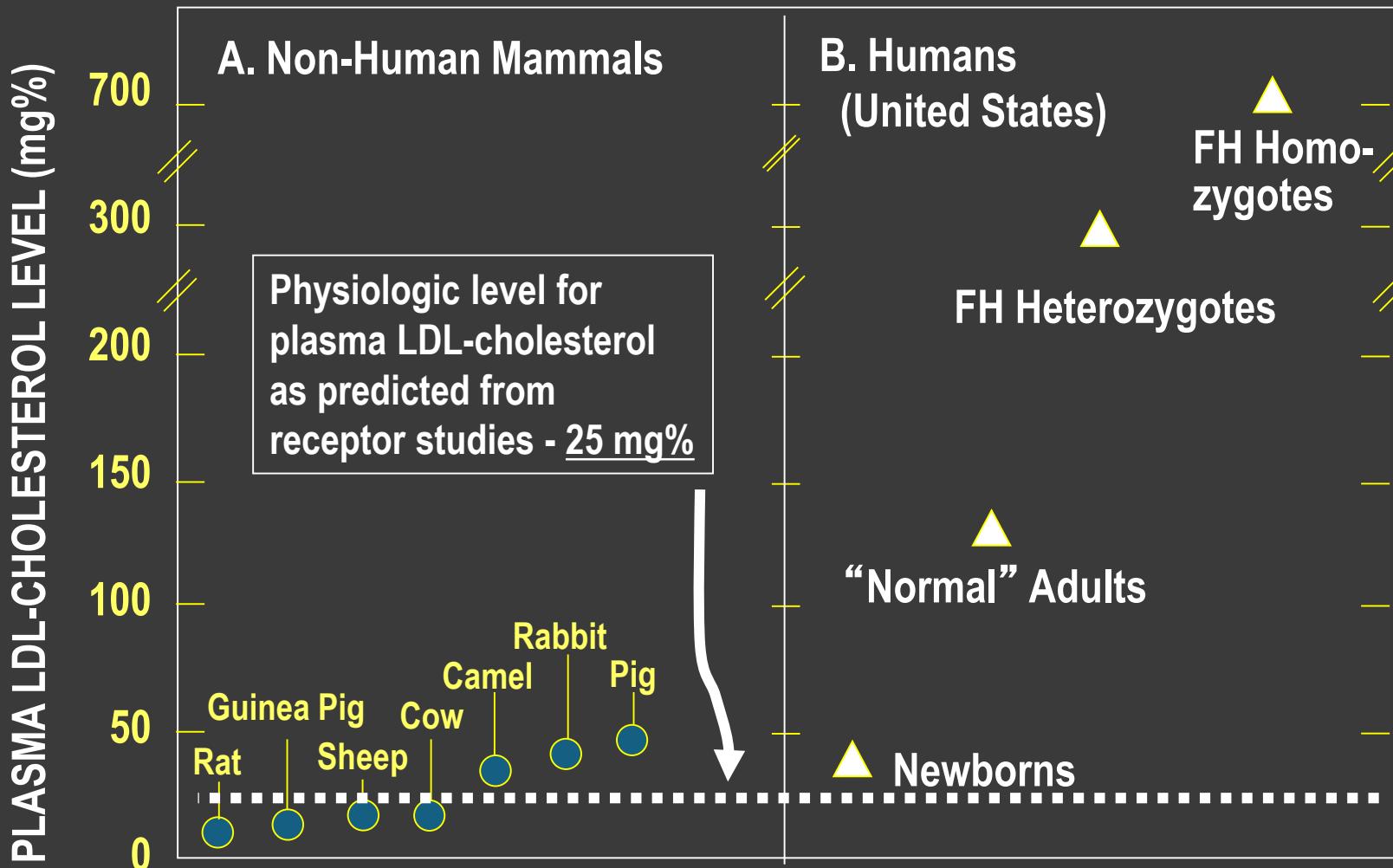
Il sottoscritto Arrigo F.G. Cicero ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

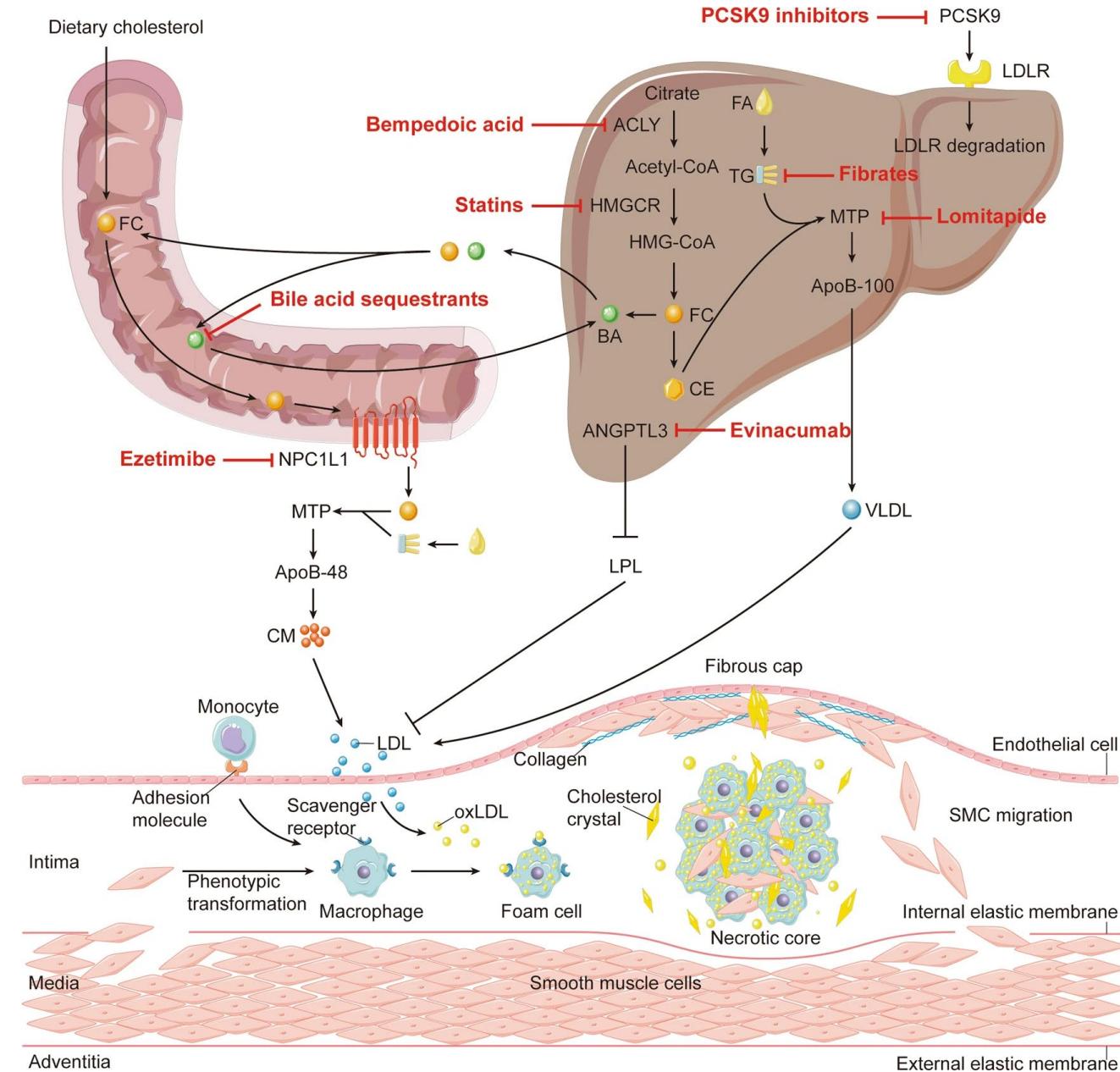
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Dr. Schaer
- Sharper
- Menarini
- Named
- Zentiva

LDL-C LEVELS IN HUMANS AND NON-HUMAN MAMMALS



LDL metabolism



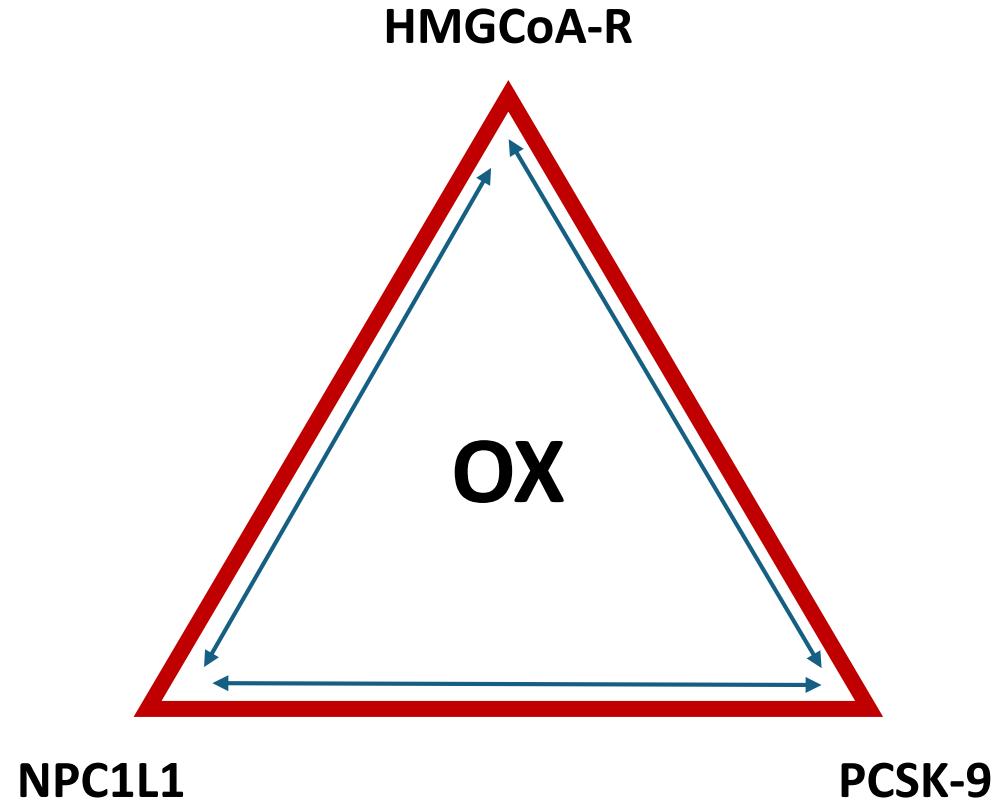
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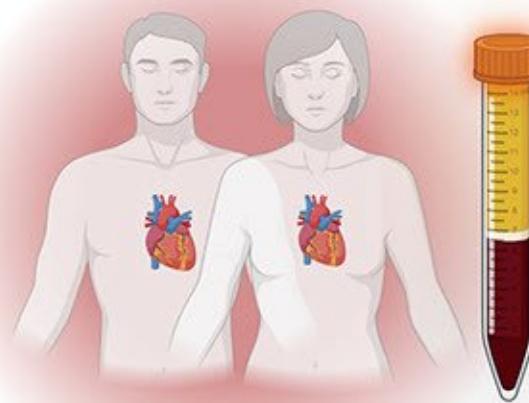
12-14 settembre 2024

Bologna

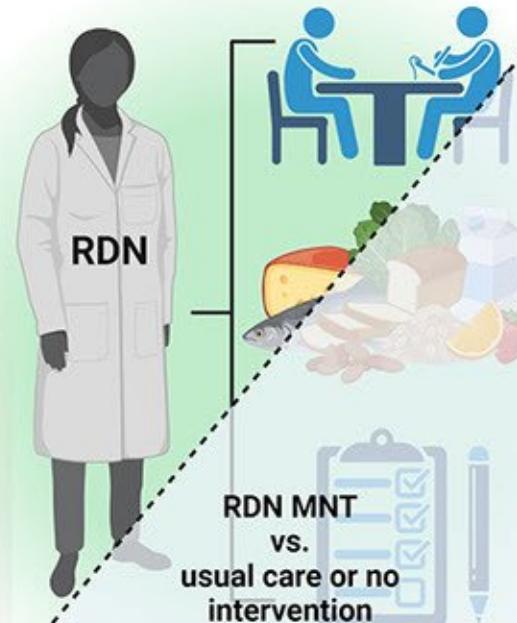


Systematic Review: Effectiveness of Medical Nutrition Therapy (MNT) for Managing Dyslipidemia

Research Question
 In adults with dyslipidemia, what is the effectiveness of MNT provided by a registered dietitian nutritionist (RDN), compared to usual care or no intervention, on lipid levels?



Intervention & Comparison



Primary CVD risk factor = **Dyslipidemia**

Search Results

Databases Searched:
 MEDLINE
 CINAHL
 Cochrane CENTRAL
 Cochrane Systematic Reviews

Full text articles screened = 89
 Included RCTs = 7
 Total n = 838

Intervention Characteristics

Provider	RDN alone (n = 3) Multidisciplinary team (n = 4)
Intervention Duration	8 to 12 months
# of contacts with RDN	2 to 12 in-person
Contact duration	30 to 120 minutes
Type of session	Individual session (n = 2) Group session (n = 1) Group + individual session (n = 4)

Meta-analysis Results Reported as mean difference ($\pm 95\% \text{ CI}$)		Certainty of Evidence
Total Cholesterol	-20.84 mg/dL (-40.60, -1.07), P = 0.04	⊕⊕⊕ MODERATE
Triglycerides	-32.55 mg/dL (-57.78, -7.32), P = 0.01	⊕⊕⊕ MODERATE
LDL Cholesterol	-11.56 mg/dL (-21.10, -2.03), P = 0.02	⊕⊕⊕ MODERATE
HDL Cholesterol	1.75 mg/dL (-1.43, 4.92), P = 0.28	⊕⊕ LOW

Conclusion
 In adults with dyslipidemia, MNT provided by a RDN is effective for improving lipid levels, compared to usual care or no intervention.

Pharmacological Research 183 (2022) 106402



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Contents lists available at ScienceDirect

Pharmacological Research

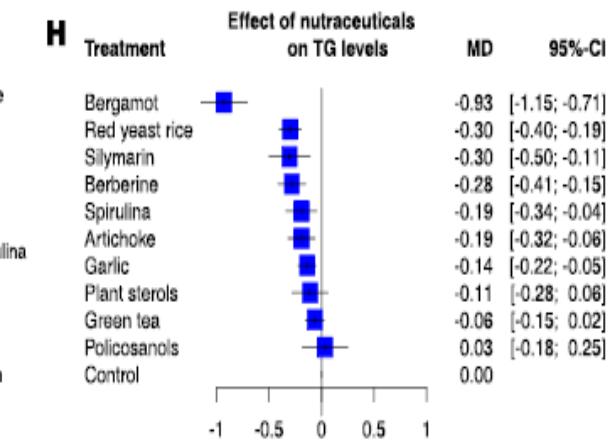
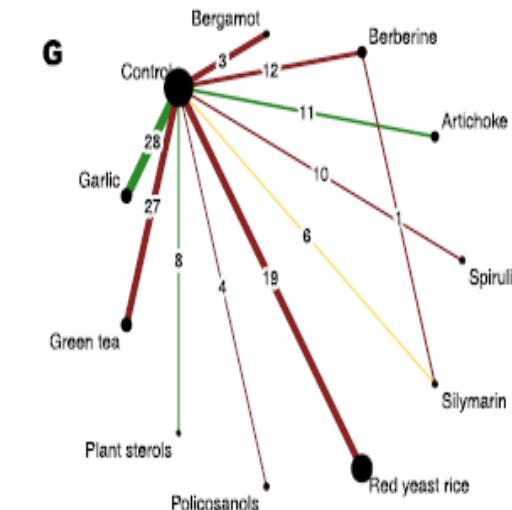
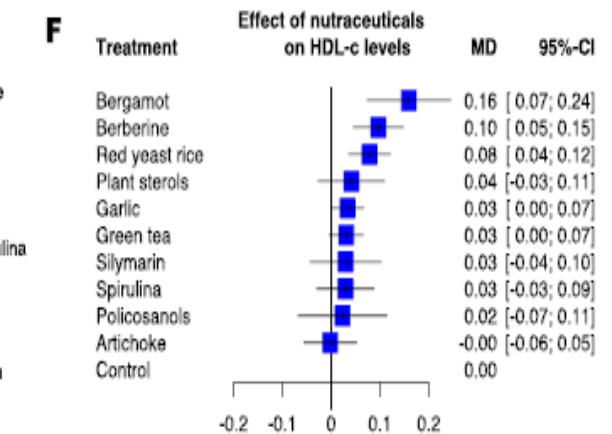
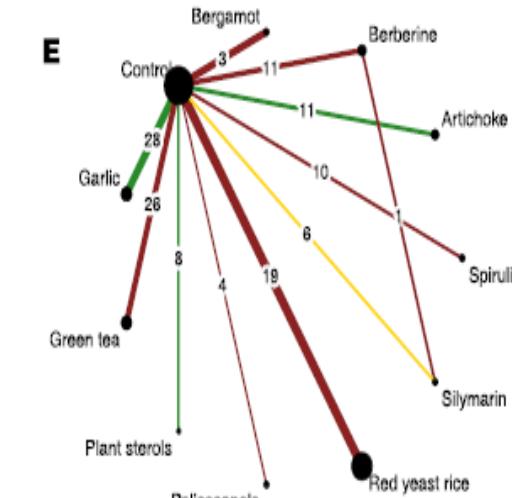
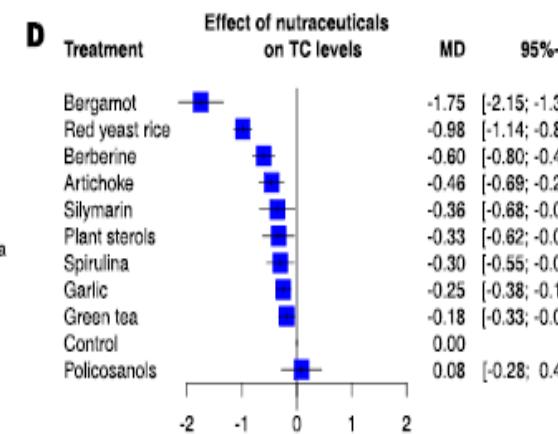
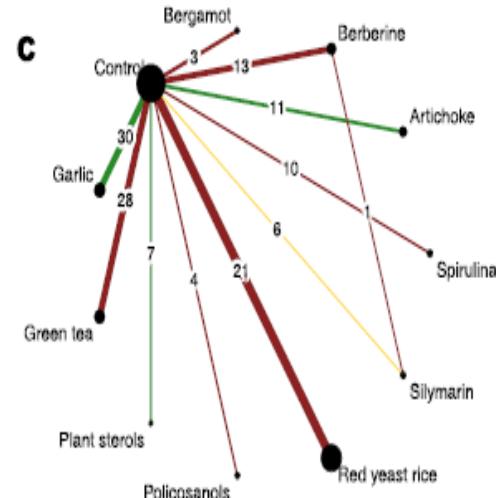
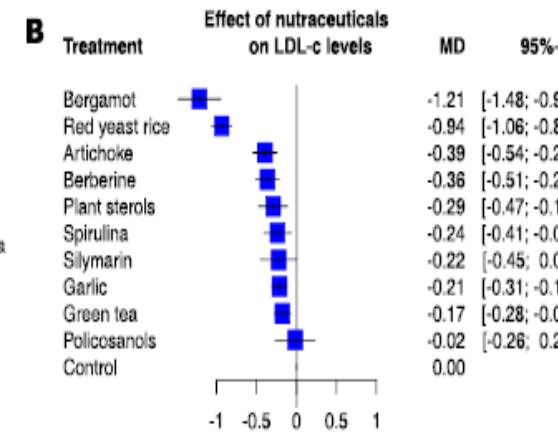
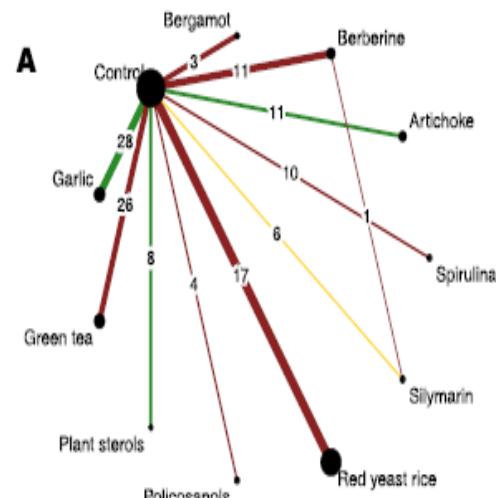
journal homepage: www.elsevier.com/locate/yphrs

Review

A network meta-analysis on the comparative effect of nutraceuticals on lipid profile in adults



Tadeusz Osadnik ^a, Marcin Goławski ^a, Piotr Lewandowski ^a, Jakub Morze ^b, Kamila Osadnik ^a, Natalia Pawlas ^a, Mateusz Lejawa ^a, Grzegorz K. Jakubiak ^{a,c}, Agnieszka Mazur ^a, Lucas Schwingschackl ^d, Mariusz Gąsior ^e, Maciej Banach ^{f,*}



14°

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12-14 settembre 2024

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L' IDROCLORATO DI BERBERINA

NEL TUMORE DELLA MILZA DA INFESTAZIONE
DI MALARIA

DEL DOTTOR CAVALLIERE

PAOLO MACHIAVELLI

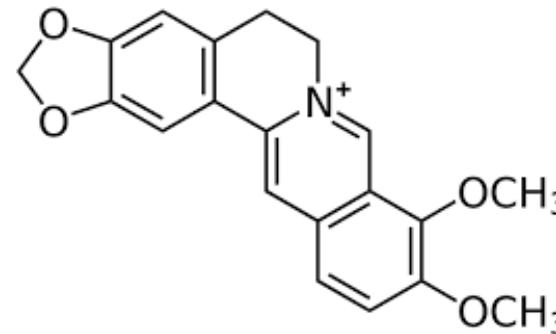
Medico capo nell'Esercito italiano.

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—
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MILANO

*Presso la Società per la pubblicazione degli Annali Universali
delle Scienze e dell'Industria
nella Galleria Du-Cristoforo*

1870.



Sources

Roots, rhizomes and stem bark of:

- *Berberis* [e.g. *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric)]
- *Hydrastis canadensis* (goldenseal)
- *Xanthorhiza simplicissima* (yellow root)
- *Phellodendron amurense* (Amur corktree)
- *Coptis chinensis* (Chinese goldthread)
- *Tinospora cordifolia*
- *Argemone mexicana* (prickly poppy)
- *Eschscholzia californica* (Californian poppy)

Chemical characteristics:

- Quaternary ammonium salt from the group of isoquinoline alkaloid (2,3–methylenedioxy-9,10-dimethoxyprotoberberine chloride; C₂₀H₁₈NO₄⁺)
- Molar mass = 336.36122 g/mol

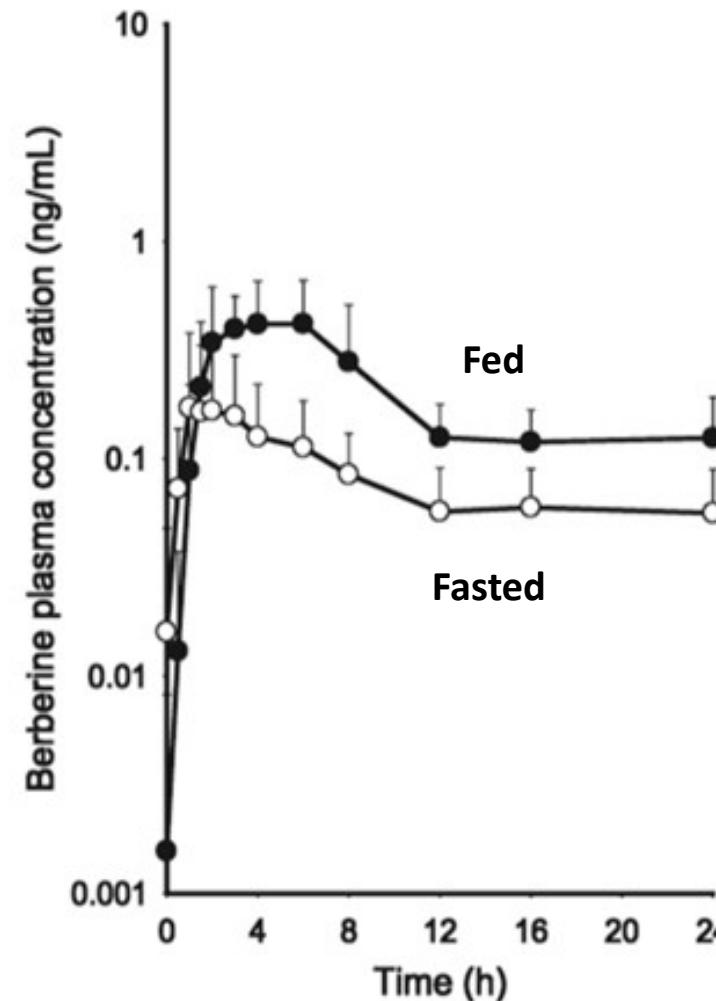
Cicero AF et al. Expert Opin Drug Saf. 2012;11(5):753-66.

Pharmacological characteristics

- Low oral bioavailability (<5%): bowel P-glycoprotein appears to contribute its poor absorption actively expelling the alkaloid from the lumen mucosal cells
- After a single administration the C_{max} is 394.7 µg·L⁻¹, the t_{peak} 2.37 h, and the AUC 0-∞ 3028 3 µg·L⁻¹ ·h⁻¹.
- Strong affinity for albumin: it could displace drugs like warfarin, thiopental, and tolbutamide, whose plasma level so increases as their toxicity
- In a similar way, berberine displaces bilirubin from albumin
- Berberine is metabolized by p450 enzyme system in liver
- Berberine may inhibit p450 2E1 and 1A2: not related to a significant increase in pharmacological interaction risk
- On the other side, berberine can markedly increase blood levels of cyclosporine A increasing its bioavailability, while reducing its metabolism
- Safety in pregnancy: not known

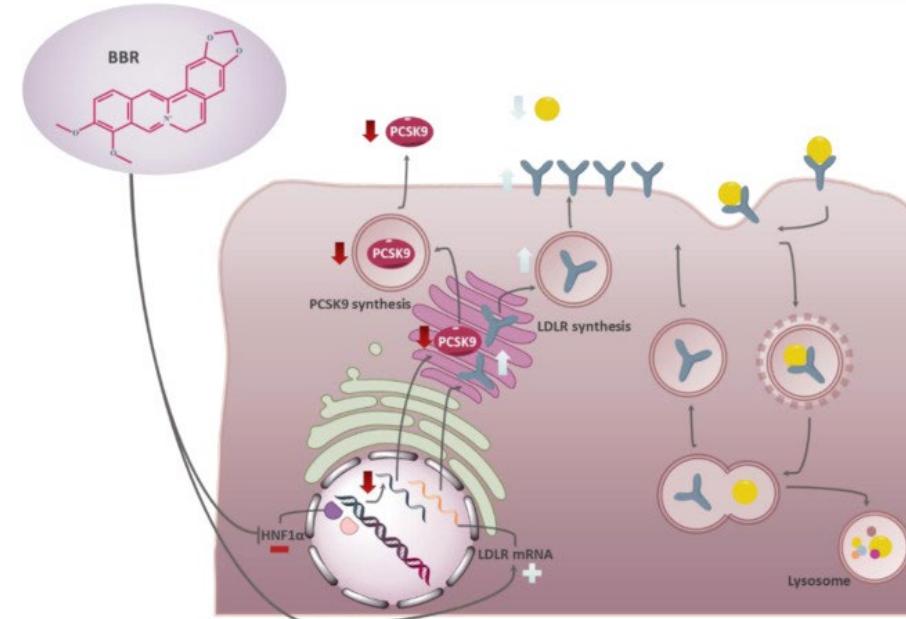
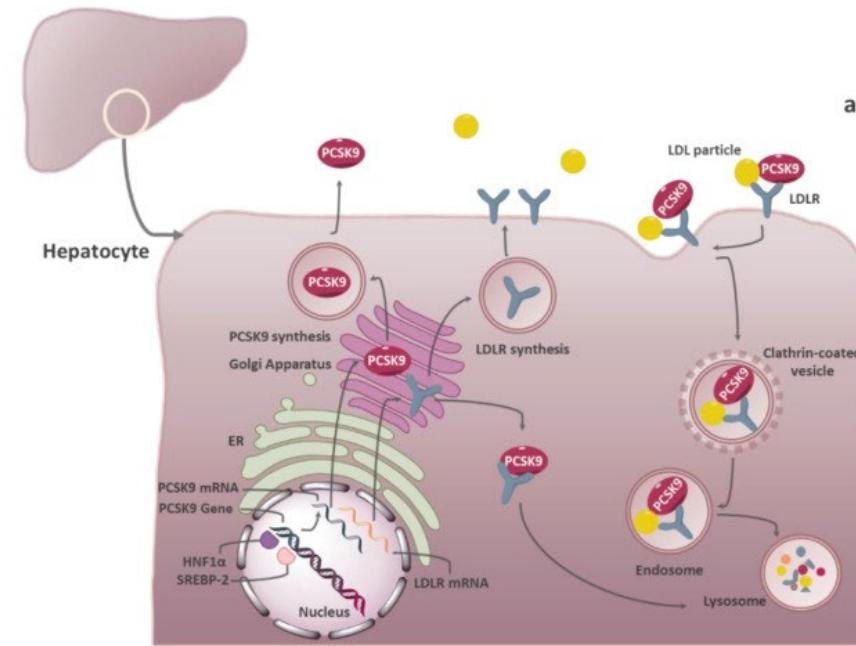
Cicero AF et al. *Food Funct.*
2017;8(6): 2076-88.

Effects of food on oral bioavailability of berberine in healthy men



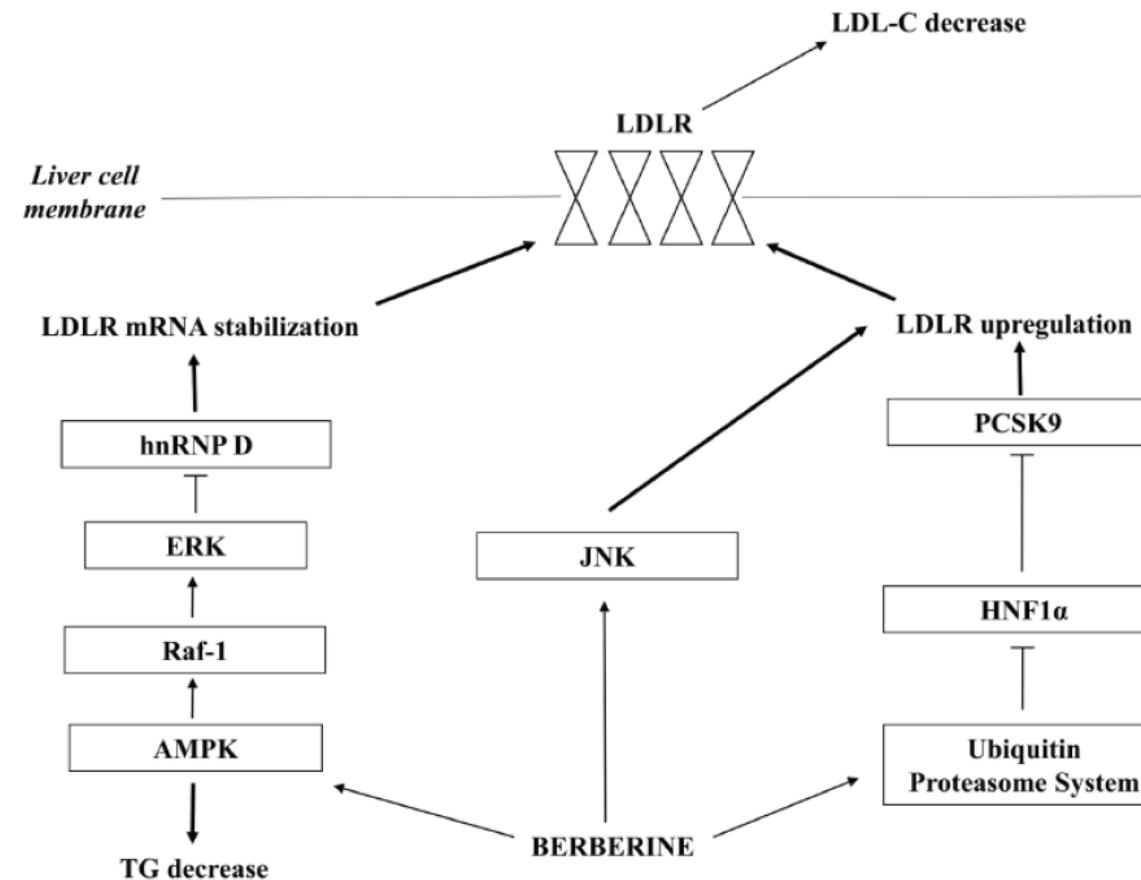
Persiani S et al. J Pharm
Pharmacol 2014;2:703-712.

PCSK9 functions with or without presence of berberine.



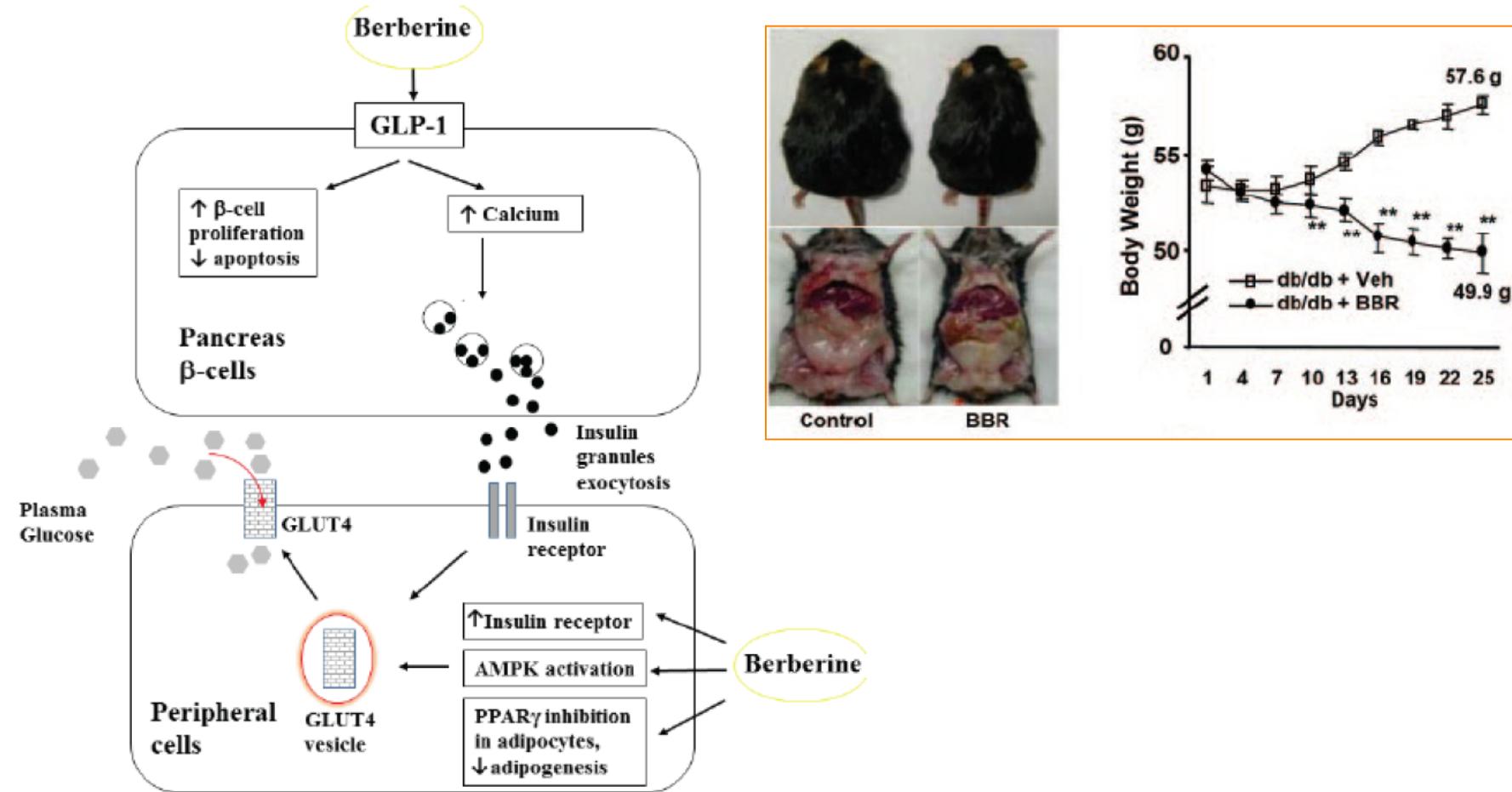
EXCLI J. 2022 Aug 17;21:1099-1110.

Berberine: the lipid lowering action



Cicero AF et al.
Curr Med Chem.
2016;23(14):1460-76.

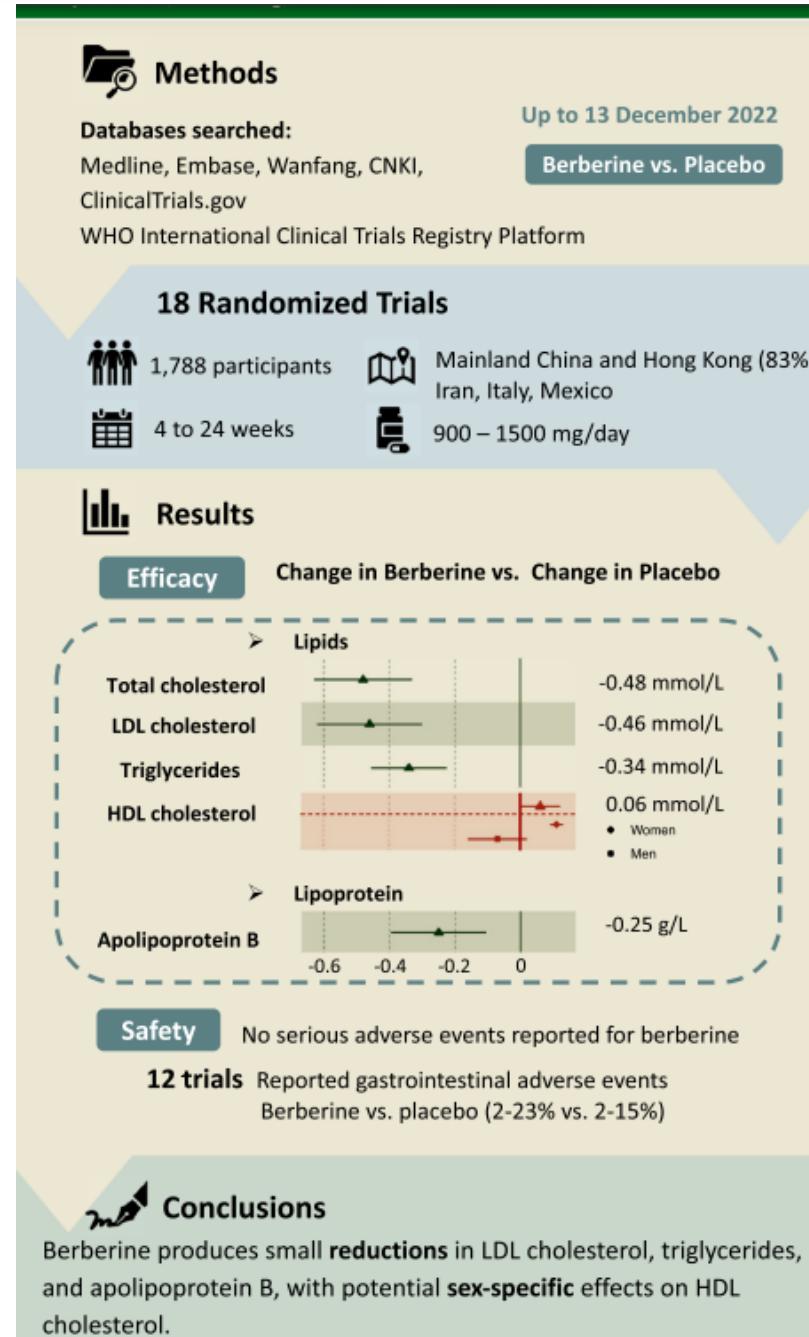
Berberine and insulin-resistance



Lee YS et al. Diabetes 2006;55:2256–2264.

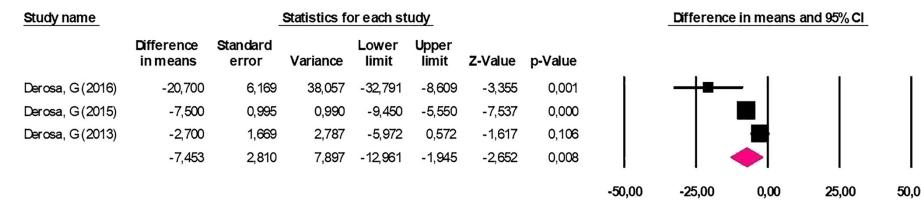
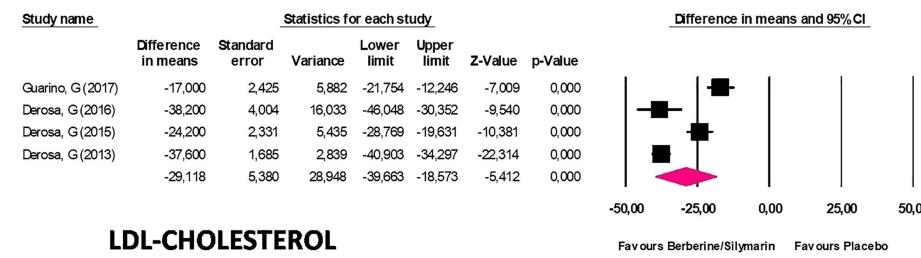
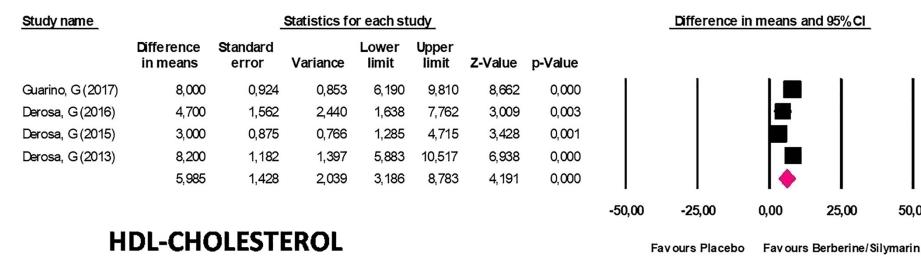
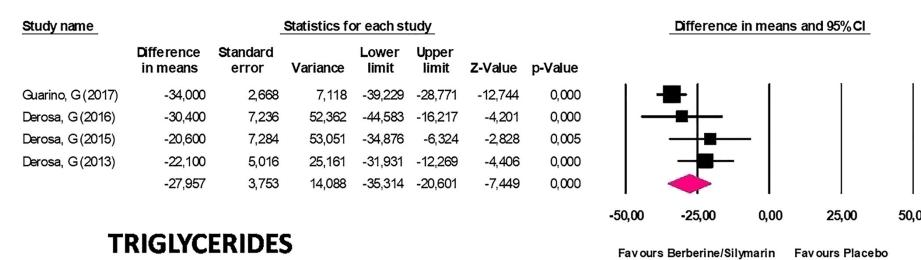
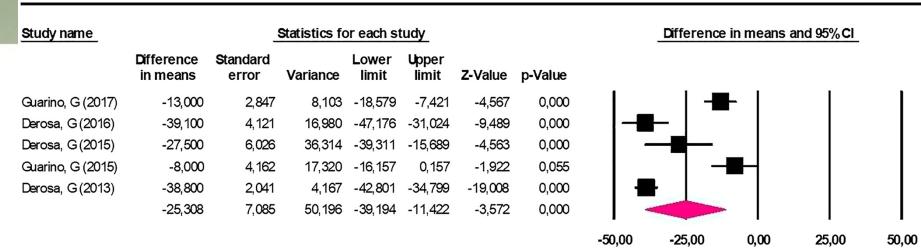
The effects of berberine on blood lipids: a systemic review and meta-analysis of RCTs

Drugs. 2023 Apr;83(5):403-427.

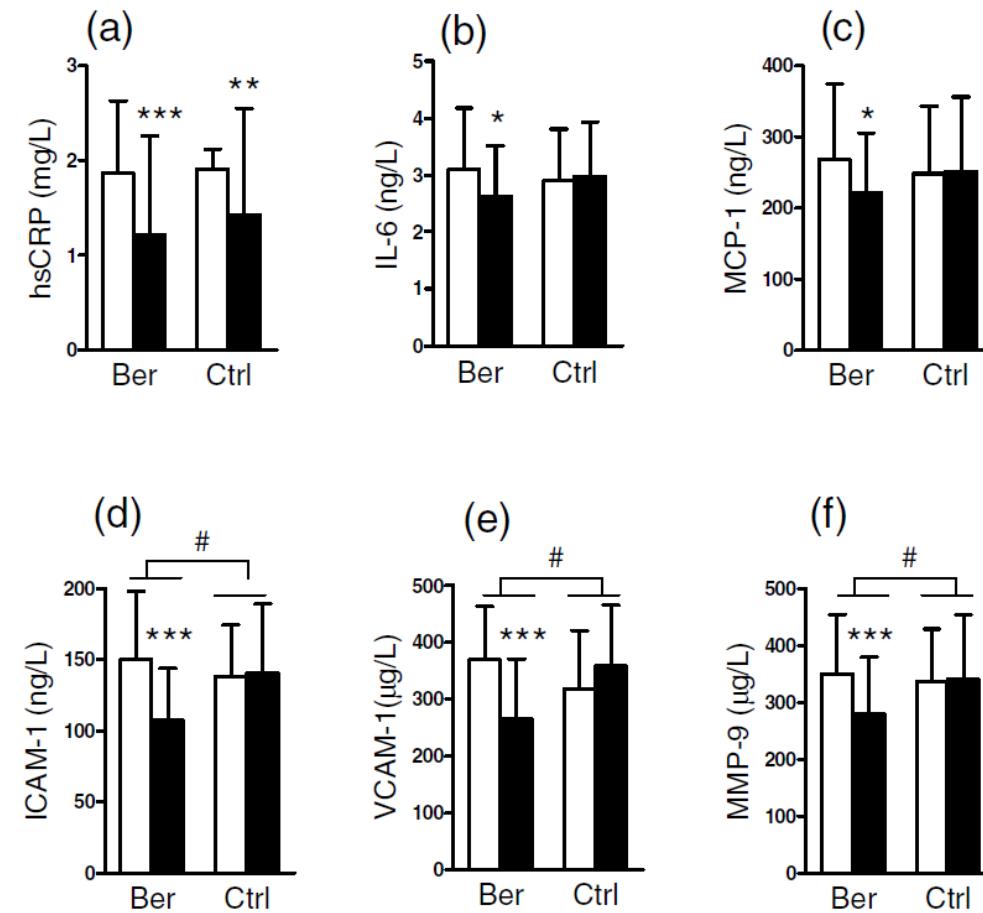


Metabolic effect of berberine-silymarin association: A meta-analysis of randomized, double-blind, placebo-controlled clinical trials

Fogacci F, Grassi D, Rizzo M, Cicero AFG.
Phytother Res. 2019 Apr;33(4):862-870.

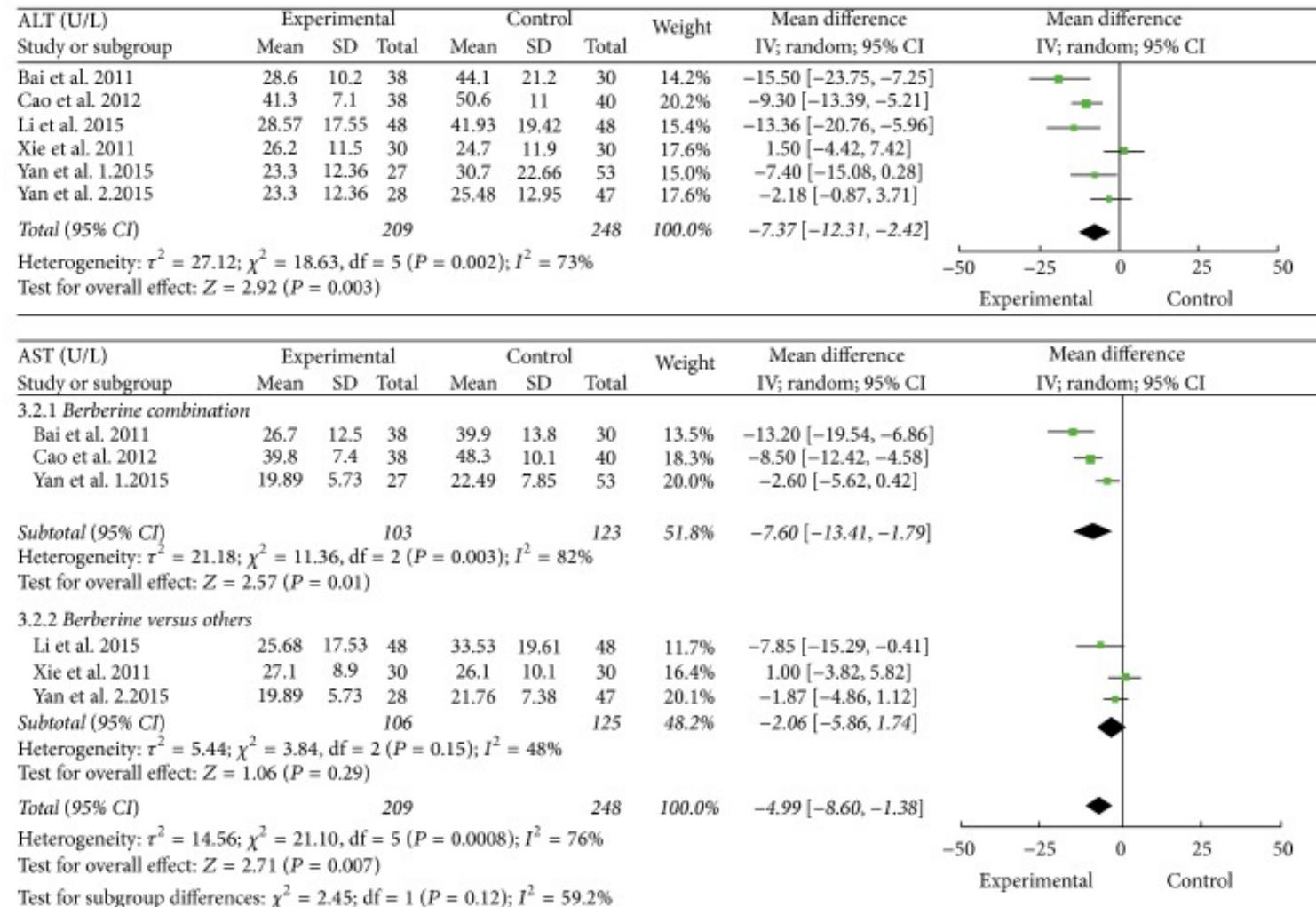


Effects of berberine on vascular inflammation biomarkers in CAD patients after PTCA



Clin Exp Pharmacol Physiol
2012;39(5):
406-11.

Effects of berberine on liver transaminases in NAFLD subjects



Evid Based CAM.
2016;2016:3593951.

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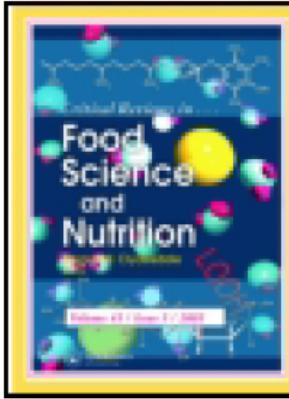
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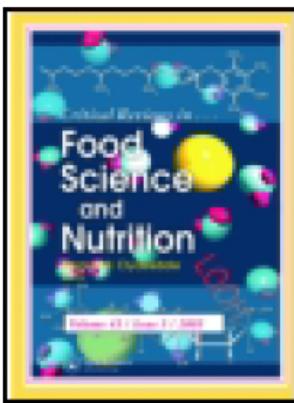
Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: <http://www.tandfonline.com/loi/bfsn20>

Lipid-lowering activity of artichoke extracts: a systematic review and meta-analysis

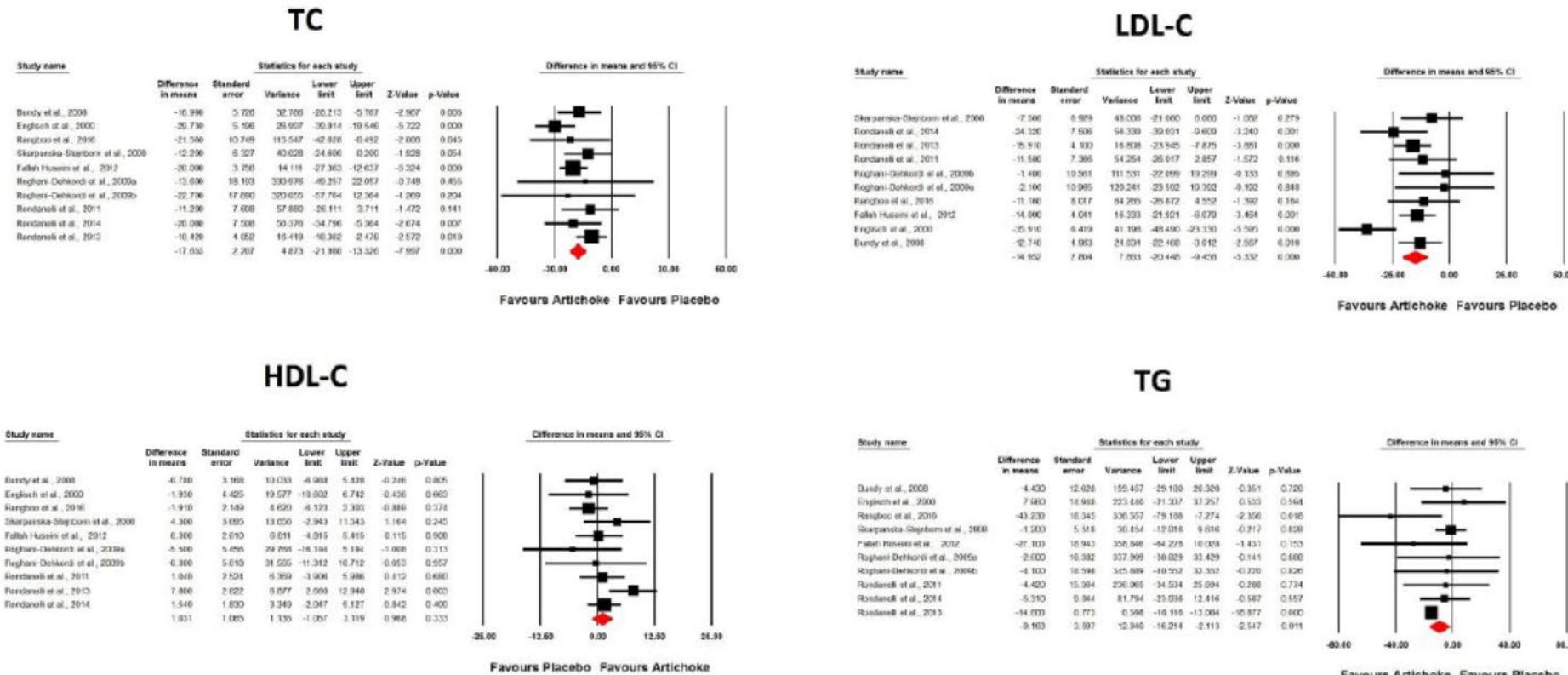
Amirhossein Sahebkar, Matteo Pirro, Maciej Banach, Dimitri P. Mikhailidis,
Stephen L. Atkin & Arrigo F.G. Cicero

To cite this article: Amirhossein Sahebkar, Matteo Pirro, Maciej Banach, Dimitri P. Mikhailidis,
Stephen L. Atkin & Arrigo F.G. Cicero (2017): Lipid-lowering activity of artichoke extracts: a
systematic review and meta-analysis, Critical Reviews in Food Science and Nutrition, DOI:
[10.1080/10408398.2017.1332572](https://doi.org/10.1080/10408398.2017.1332572)

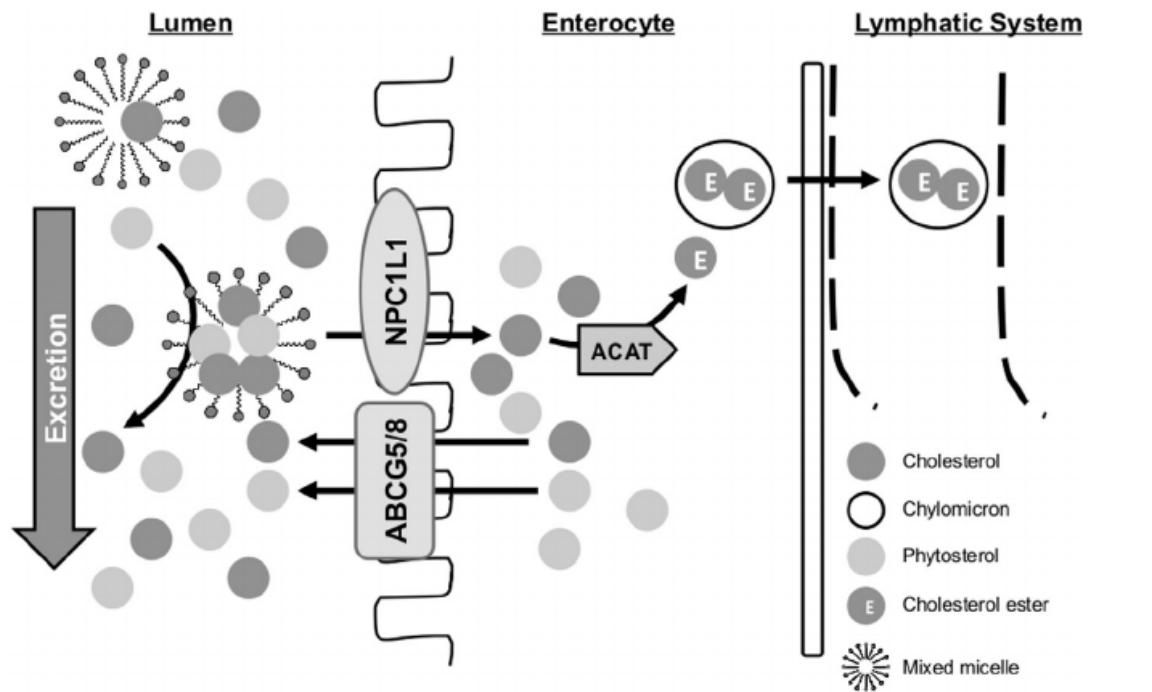
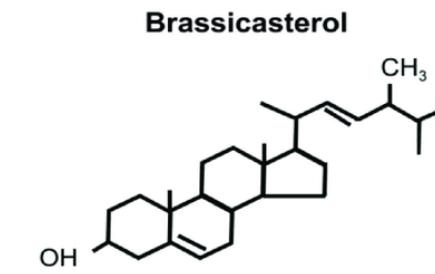
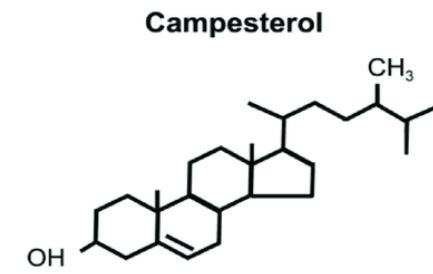
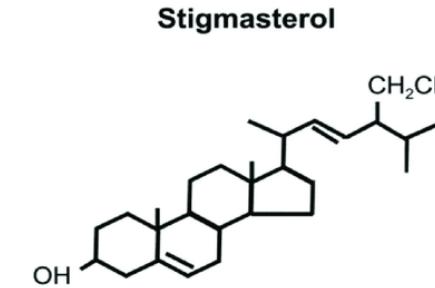
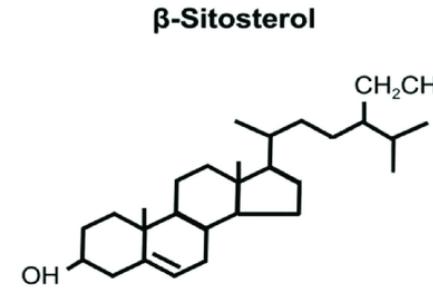


Critical Reviews in Food Science and Nutrition

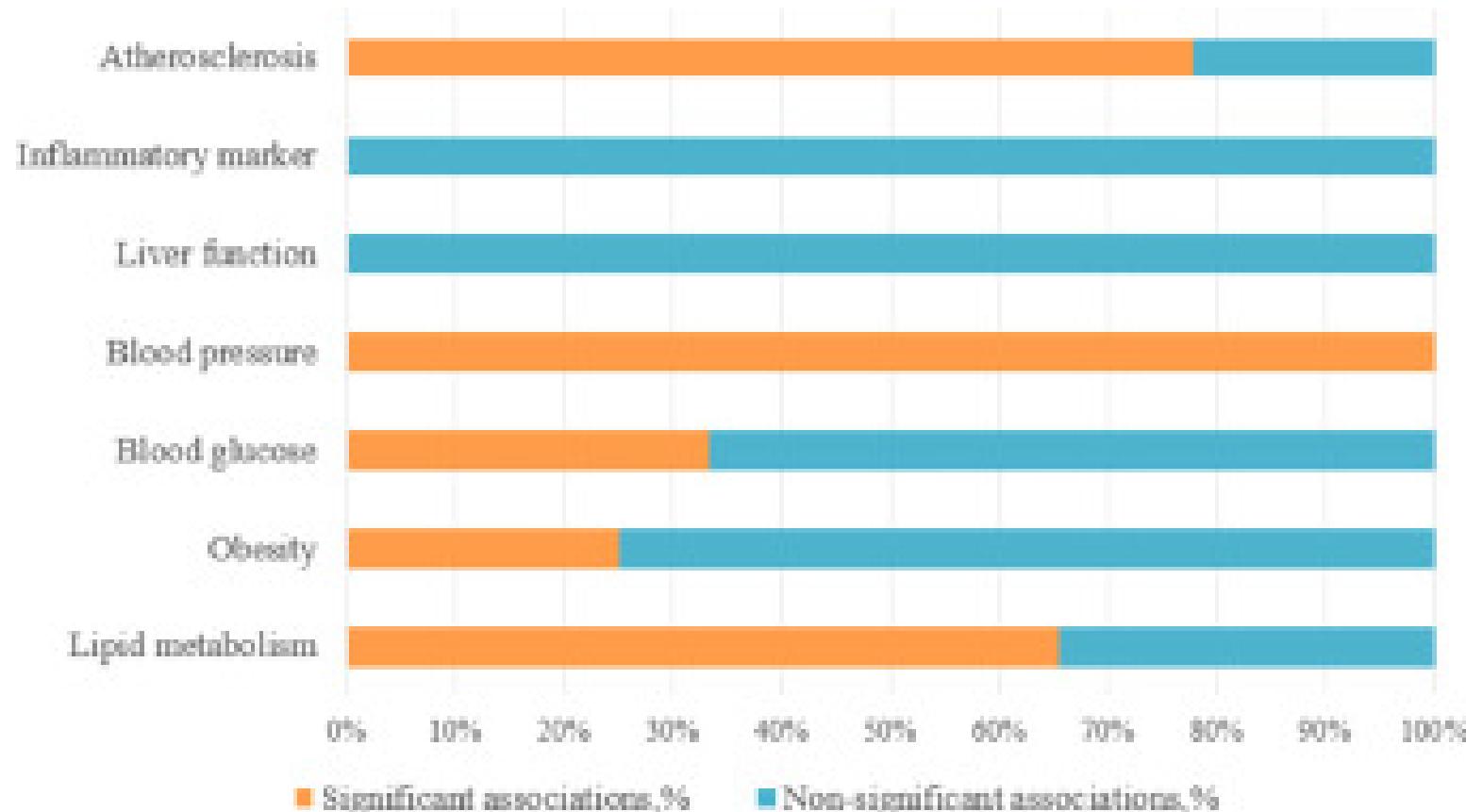
ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: <http://www.tandfonline.com/loi/bfsn20>



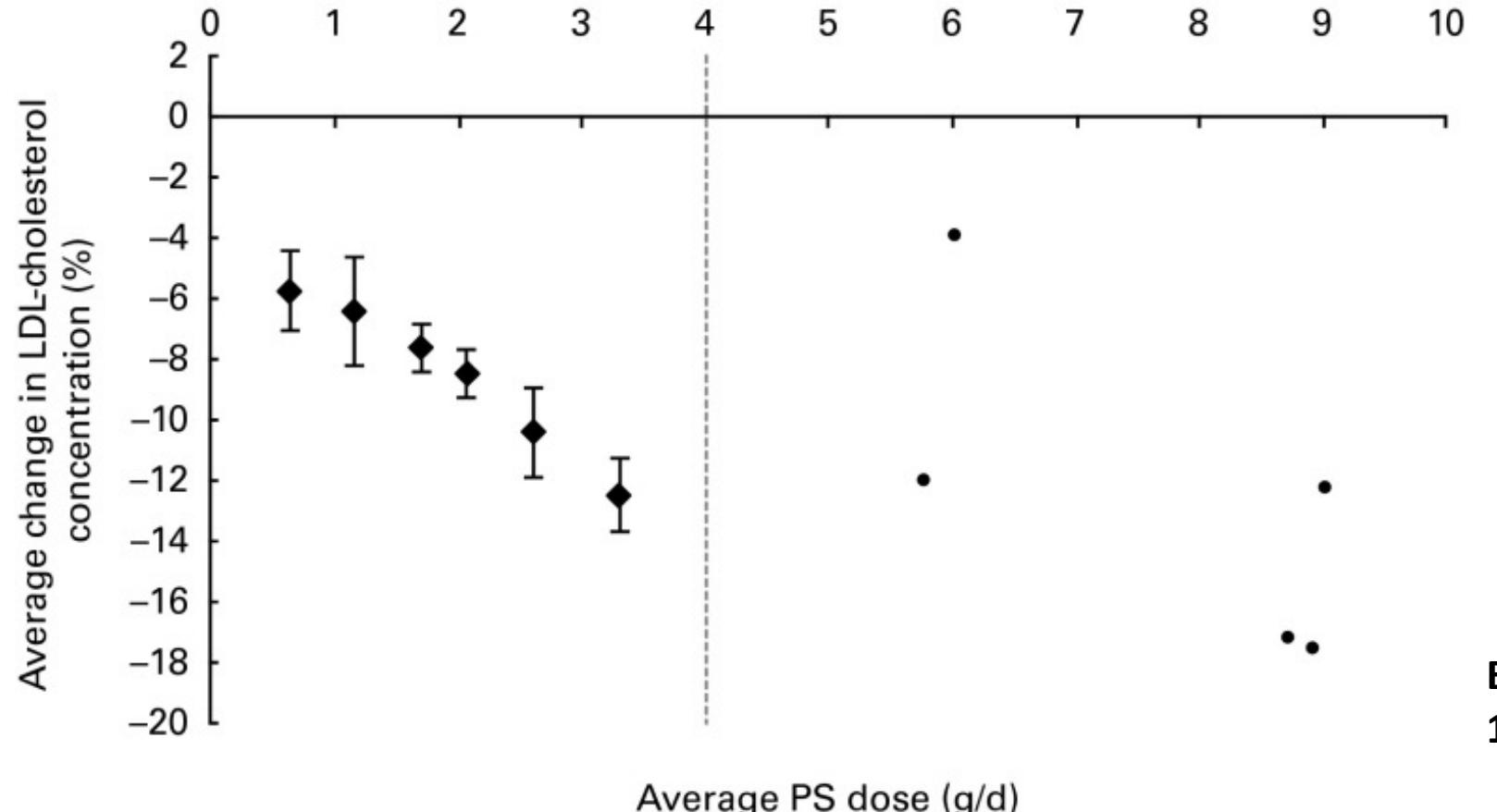
Phytosterols and Cholesterol absorption



Map of outcomes related to consumption of phytosterols



Average effects on LDL-C concentration for different dose ranges of phytosterols

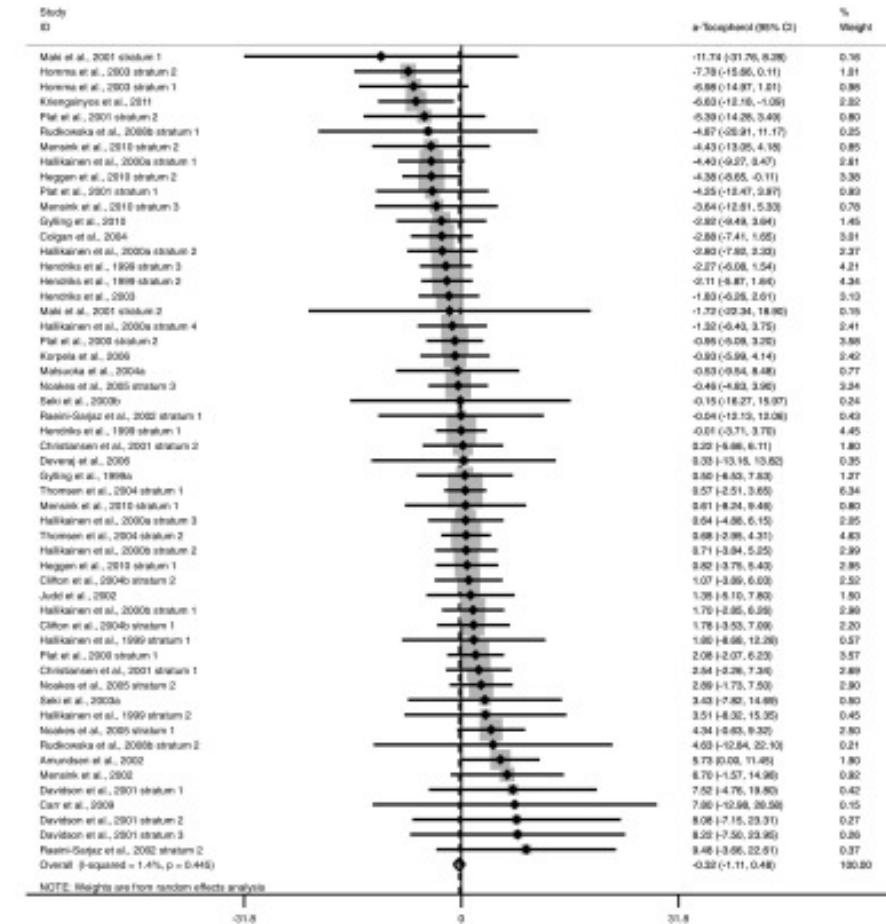
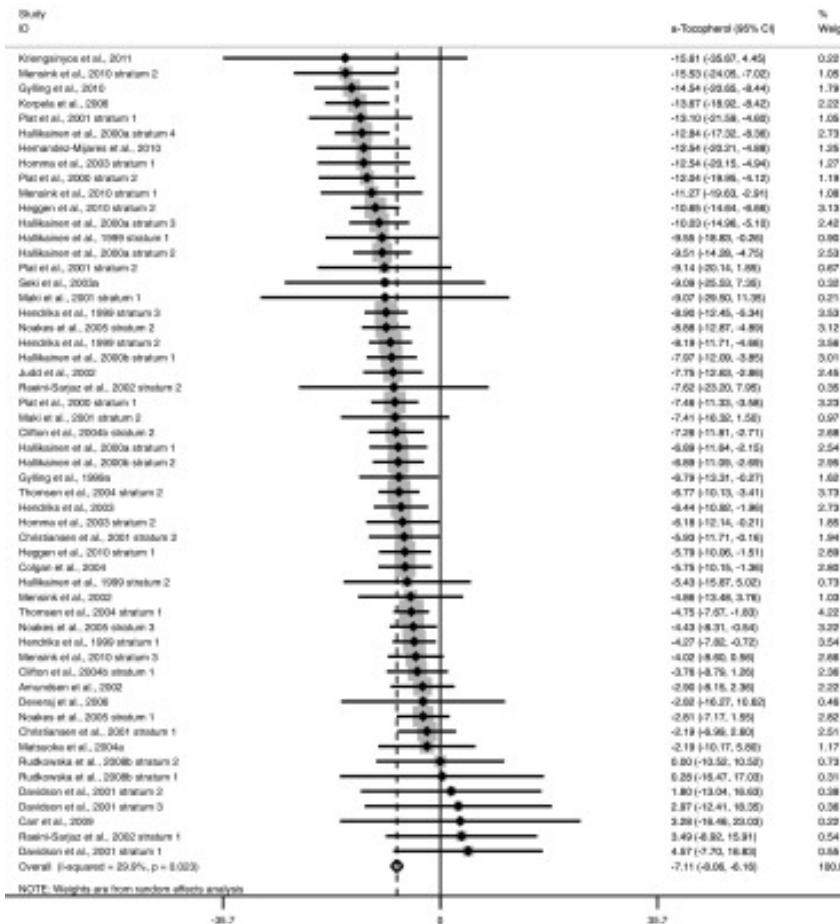


Br J Nutr. 2014;
112(2):214–219.

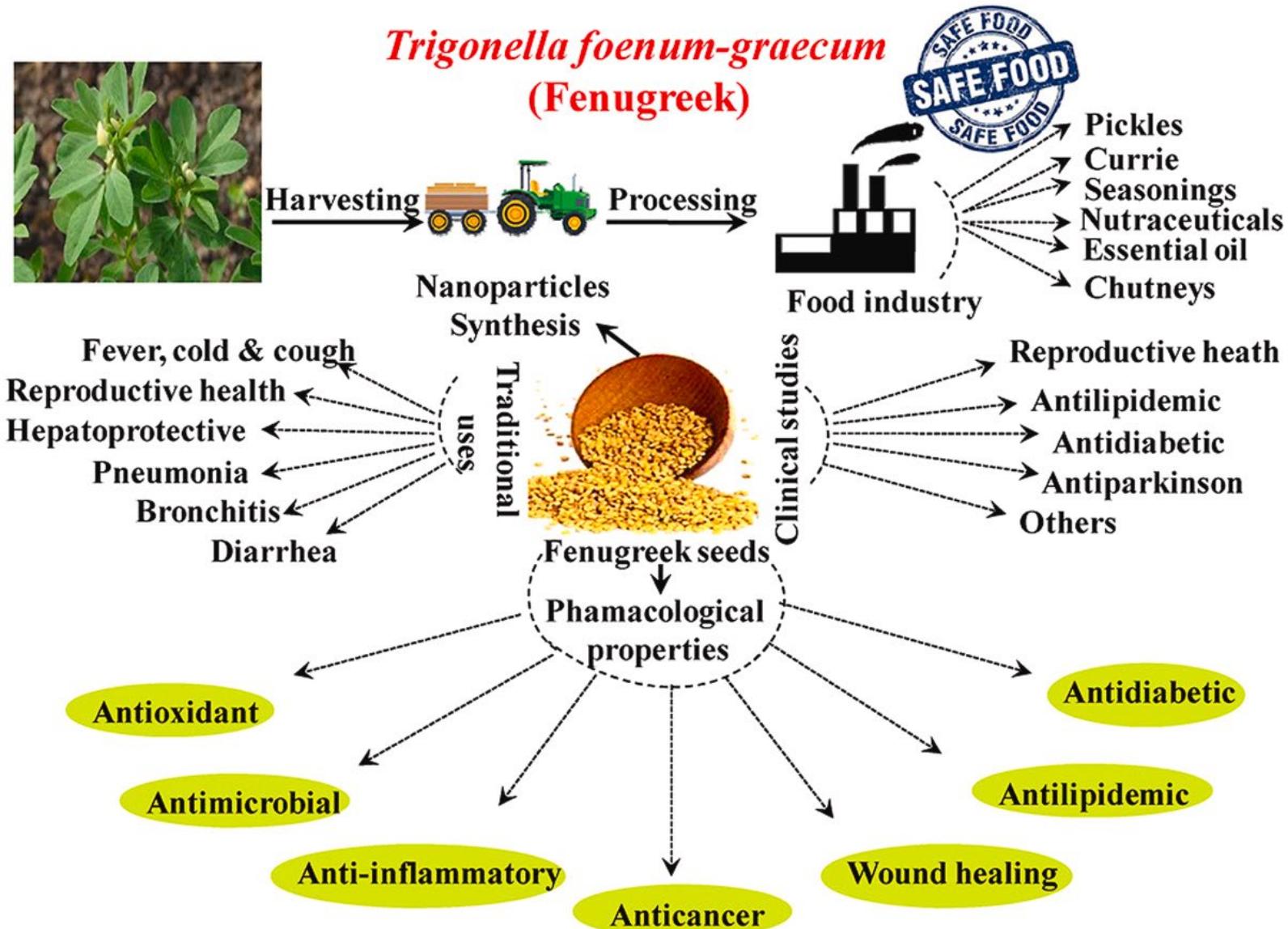
Vantaggi dei fitosteroli

- Virtualmente privi di effetti collaterali
- Virtualmente privi di interazioni farmacologiche
- Non assorbiti (= utilizzabili anche in gravidanza ed età pediatrica)
-
- Dubbi: - Beta-sitostolemia
 - Assorbimento vitamine liposolubili (?)

Relative change in non-standardized (*left*) and TC-standardized (*right*) plasma α -tocopherol concentrations



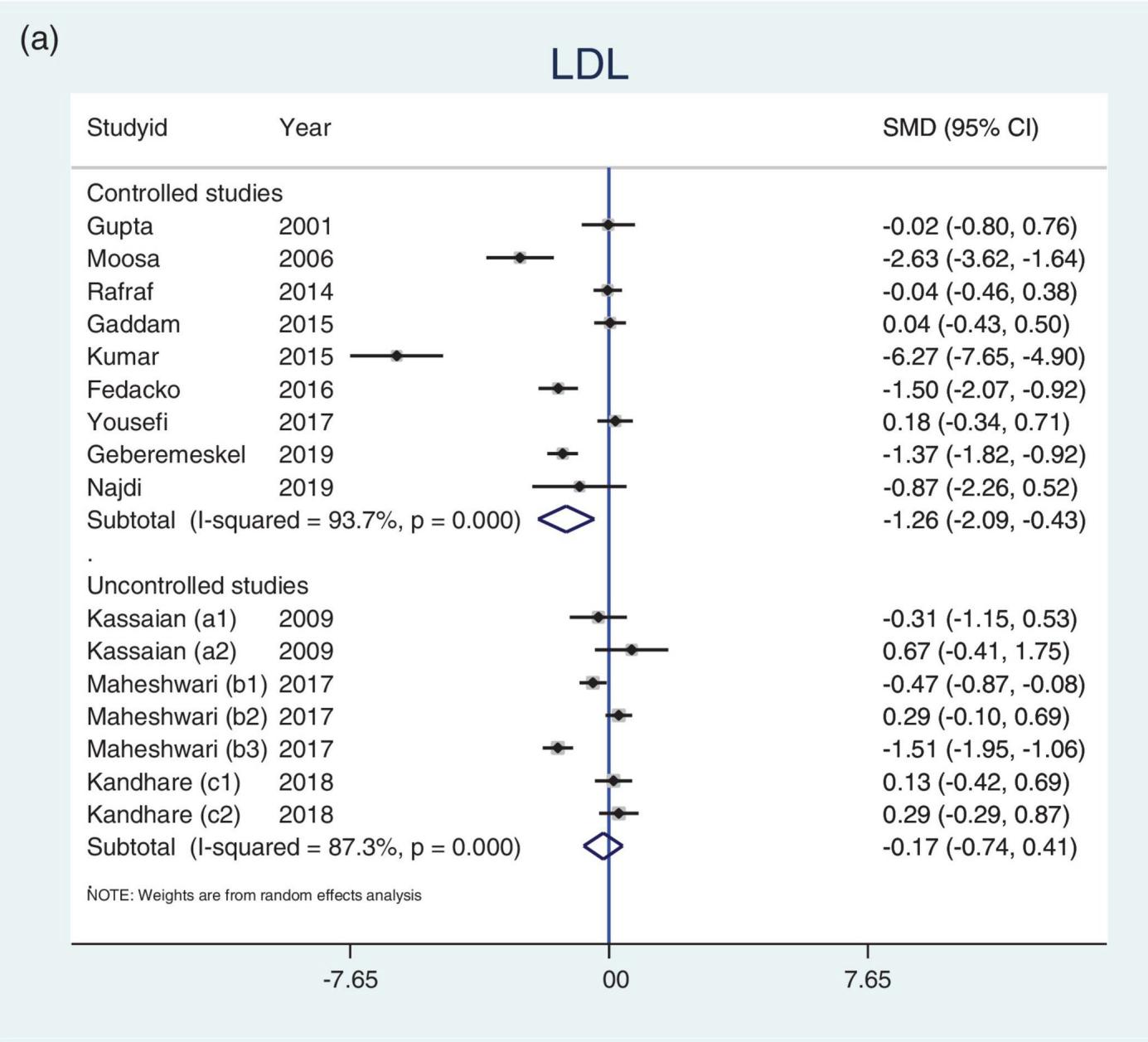
Eur J Nutr. 2017;
56(3): 909–923.



Effect of fenugreek consumption on serum lipid profile: A systematic review and meta-analysis

Phytother Res. 2020;
34(9):2230-2245.

(a)



Article

Hydroxytyrosol-Rich Olive Extract for Plasma Cholesterol Control

Arrigo F. G. Cicero ^{1,2,*}, Federica Fogacci ^{1,2}, Antonio Di Micoli ¹, Maddalena Veronesi ¹, Elisa Grandi ¹
and Claudio Borghi ¹

¹ Hypertension and Cardiovascular Risk Research Group, Medical and Surgical Sciences Department, University of Bologna, 40100 Bologna, Italy

² Italian Nutraceutical Society (SINut), 40100 Bologna, Italy

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Abstract: Emerging research and epidemiological studies established the health benefits of the Mediterranean diet, whose hallmark is the high consumption of olives and olive oil as the primary source of dietary fatty acids and major sources of antioxidants. The aim of this study was to evaluate the effect of daily dietary supplementation with highly standardized polyphenols—mainly hydroxytyrosol—which are derived from olive oil production by-products of an Italian olive variety (Coratina Olive) on the plasma cholesterol of a sample of hypercholesterolemic individuals. This single-arm, non-controlled, non-randomized, prospective pilot clinical study involved a sample of 30 volunteers with polygenic hypercholesterolemia. The study design included a 2-week run-in and a 4-week intervention period. Patients were evaluated for their clinical status and by the execution of a physical examination and laboratory analyses before and after the treatment. The intervention effect was assessed using Levene's test followed by the independent Student's *T* test after the log-transformation of the non-normally distributed continuous variables. Dietary supplementation with highly standardized polyphenols that are derived from Coratina Olive (namely SelectSIEVE® OptiChol) was associated with a significant improvement in systolic blood pressure, pulse pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, non-HDL-C, fasting plasma glucose, and uric acid compared to baseline values. Furthermore, SelectSIEVE® OptiChol was well tolerated by volunteers. We acknowledge that the study has some limitations, namely the small patient sample, the short follow-up, and the lack of randomization and control procedures. However, these results are consistent with previous literature that referred to extracts from different olive varieties. Definitely, our observations lay further foundations for the use of polyphenolic-rich olive extract from Coratina Olive in the prevention and treatment of first-stage metabolic syndrome.

Citation: Cicero, A.F.G.; Fogacci, F.; Di Micoli, A.; Veronesi, M.; Grandi, E.; Borghi, C. Hydroxytyrosol-Rich Olive Extract for Plasma Cholesterol Control. *Appl. Sci.* **2022**, *12*, 10086. <https://doi.org/10.3390/app121910086>

Academic Editor: Alessandro Genovese

Received: 12 August 2022

Accepted: 5 October 2022

SelectSIEVE® OptiChol
(N. 30)

Parameters	SelectSIEVE® OptiChol (N. 30)			p-Value versus Baseline
	Pre-Run-in	Baseline	Week 4	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	53 ± 5			
WC (cm)	89.8 ± 5.3	88.9 ± 5.1	87.7 ± 5.5	n.s.
ICO	0.56 ± 0.08	0.54 ± 0.07	0.53 ± 0.08	n.s.
BMI (Kg/m ²)	24.8 ± 2.2	24.6 ± 2.2	24.3 ± 2.3	n.s.
SBP (mmHg)	134 ± 5	133 ± 5	130 ± 2	<0.05
DBP (mmHg)	87 ± 2	86 ± 3	86 ± 2	n.s.
PP (mmHg)	47 ± 2	47 ± 2	44 ± 2	<0.05
HR (bpm)	74 ± 4	74 ± 4	75 ± 5	n.s.
FPG (mg/dL)	88 ± 3	90 ± 3	85 ± 2	<0.05
TC (mg/dL)	248 ± 13	238 ± 12	225 ± 7	<0.05
HDL-C (mg/dL)	44 ± 3	44 ± 3	48 ± 2	<0.05
LDL-C (mg/dL)	161 ± 8	155 ± 8	145 ± 5	<0.05
Non HDL-C (mg/dL)	204 ± 11	198 ± 11	177 ± 8	<0.05
TG (mg/dL)	216 ± 19	197 ± 16	186 ± 18	n.s.
AST (mg/dL)	23 ± 3	25 ± 4	24 ± 3	n.s.
ALT (mg/dL)	22 ± 3	22 ± 3	23 ± 4	n.s.
gGT (mg/dL)	32 ± 2	33 ± 2	30 ± 5	n.s.
SUA (mg/dL)	8.5 ± 1.8	8.6 ± 1.5	7.7 ± 1.1	<0.05



**Single-centre, randomised, double-blind,
parallel-arm clinical study on the effect of
~~CARDIORITMON® COLESTEROLO~~ in
controlling LDL-C levels in adult subjects who
are overweight or with class 1 obesity.**

Average contents	per 1 cap.	per 2 cap.
Berberis aristata DC d.e. of which berberine hydrochloride	130 mg 110.5 mg	260 mg 221 mg
Phytosterols of which beta-sitosterols	100 mg 40 mg	200 mg 80 mg
Olea Europea d.e.	100 mg	200 mg
Cynara scolymus L. d.e.	75 mg	150 mg
Trigonella foenum graecum d.e.	20 mg	40 mg

Take home messages

- Il metabolismo del colesterolo è determinato da diverse vie enzimatiche che tendono a compensarsi vicendevolmente
- Associazioni di nutraceutici con diversi meccanismi d'azione possono by-passare questo meccanismo e rivelarsi più efficaci
- La loro associazione teoricamente razionale deve essere comprovata da trials clinici controllati in doppio cieco condotti in GCP