

Nutraceutici e rischio di malattia cardio-vascolare in menopausa: oltre la gestione della dislipidemia

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Ferrara, maggio 2023**

Raccomandazioni d'uso delle statine in prevenzione primaria

Solo in pazienti tra i 40 e i 75 anni con 1 o più fattori di rischio e un rischio di MCV a 10 anni del 10% o maggiore (pazienti a rischio molto alto)

JAMA | US Preventive Services Task Force | **RECOMMENDATION STATEMENT**

Statin Use for the Primary Prevention of Cardiovascular Disease in Adults US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

RECOMMENDATION The USPSTF recommends that clinicians prescribe a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD risk of 10% or greater. (B recommendation) The USPSTF recommends that clinicians selectively offer a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more of these CVD risk factors and an estimated 10-year CVD risk of 7.5% to less than 10%. The likelihood of benefit is smaller in this group than in persons with a 10-year risk of 10% or greater. (C recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality in adults 76 years or older. (I statement)

JAMA. 2022;328(8):746-753. doi:10.1001/jama.2022.13044

Statins for the prevention of cardiovascular disease

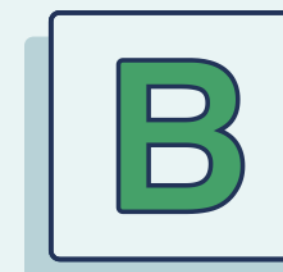
Cardiovascular disease (CVD), including heart attacks and strokes, can be prevented by treating and controlling risk factors such as dyslipidemia, high blood pressure, diabetes, and smoking.



Population

Adults aged 40 years or older without known CVD

USPSTF recommendation



The USPSTF recommends that clinicians prescribe a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors and have an estimated 10-year risk of a CVD event of 10% or greater.



Clinicians may selectively offer a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors and have an estimated 10-year risk of a CVD event of 7.5% to less than 10%.



Current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD in adults aged 76 years or older.

Statine in prevenzione primaria: editoriale

EDITORIAL

Statins for Primary Cardiovascular Disease Prevention

Time to Curb Our Enthusiasm

Anand R. Habib, MD, MPhil; Mitchell H. Katz, MD; Rita F. Redberg, MD, MSc

E' ora di frenare l'entusiasmo!

Benefici marginali e incerti in prevenzione primaria

Una sana alimentazione e l'esercizio fisico hanno effetti maggiori

upshot of myriad social determinants.^{27,28} Although statins lower LDL cholesterol in individuals, investments at the community level to construct a more salubrious environment that enables healthy eating and promotes physical activity are likely to have more widespread multiplicative and pleiotropic effects on the biological and psychosocial risks of CVD, as well as on improving quality of life. The 2022 USPSTF recommendations⁵ are an opportunity to pause and refocus efforts to meaningfully improve CVD outcomes for all, rather than extol the marginal, likely small, and uncertain absolute benefits of statins for the few in primary CVD prevention.

I nutraceutici in pazienti intolleranti alle statine

- Alcuni nutraceutici -> alternativa o terapia aggiuntiva alle statine
- Attività ipolipemizzante, oltre ad azioni protettive di altra natura (miglioramento della disfunzione endoteliale, proprietà anti-infiammatorie e anti-ossidanti)

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ABSTRACT

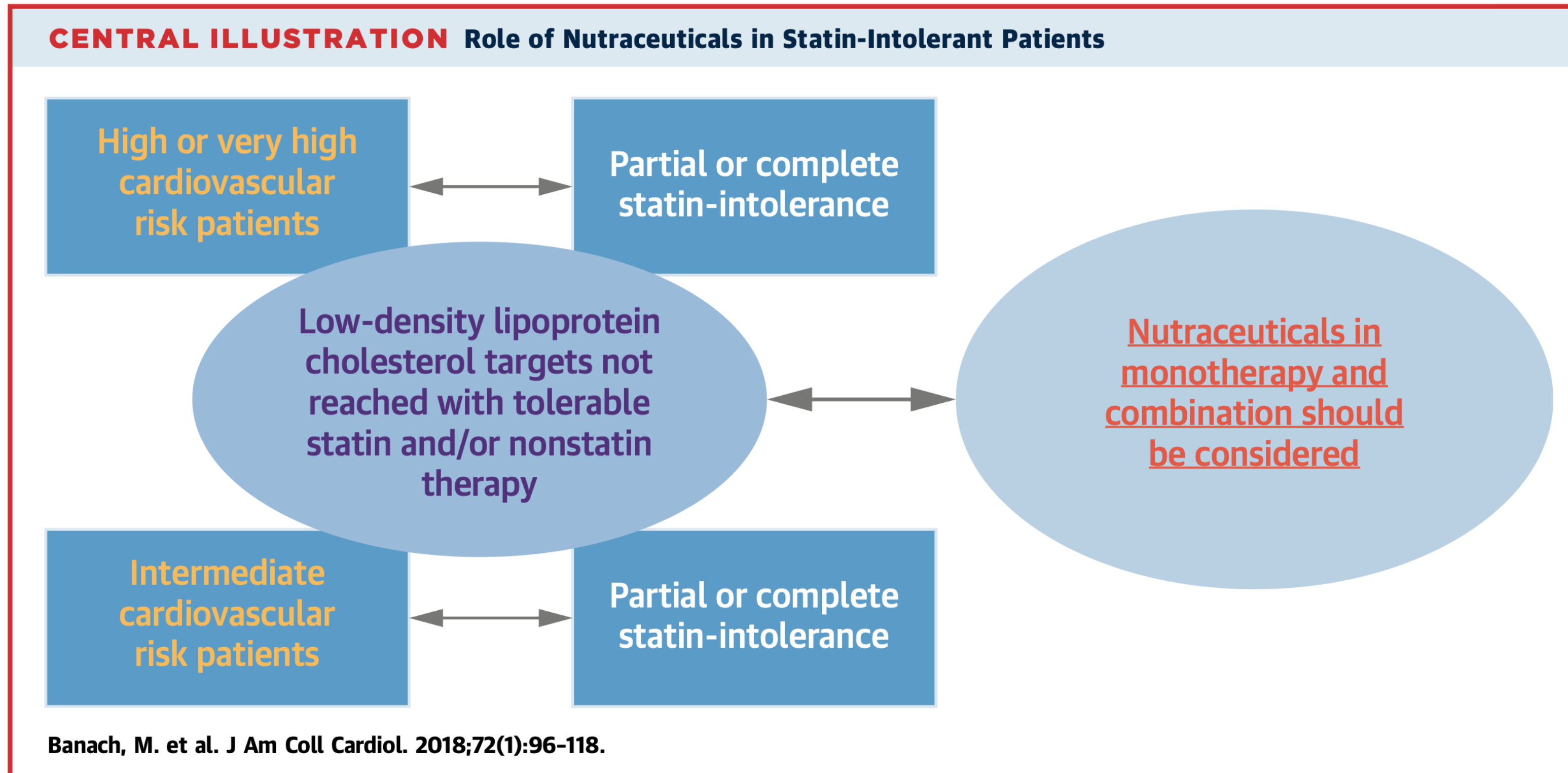
Statins are the most common drugs administered for patients with cardiovascular disease. However, due to statin-associated muscle symptoms, adherence to statin therapy is challenging in clinical practice. Certain nutraceuticals, such as red yeast rice, bergamot, berberine, artichoke, soluble fiber, and plant sterols and stanols alone or in combination with each other, as well as with ezetimibe, might be considered as an alternative or add-on therapy to statins, although there is still insufficient evidence available with respect to long-term safety and effectiveness on cardiovascular disease prevention and treatment. These nutraceuticals could exert significant lipid-lowering activity and might present multiple non-lipid-lowering actions, including improvement of endothelial dysfunction and arterial stiffness, as well as anti-inflammatory and antioxidative properties. The aim of this expert opinion paper is to provide the first attempt at recommendation on the management of statin intolerance through the use of nutraceuticals with particular attention on those with effective low-density lipoprotein cholesterol reduction. (J Am Coll Cardiol 2018;72:96-118)

JACC STATE-OF-THE-ART REVIEW

The Role of Nutraceuticals in Statin Intolerant Patients

Ruolo dei nutraceutici e livello di evidenza

Bergamotto: tra quelli segnalati



Bergamot

Ila

B

HMGF inhibits HMG-CoA reductase and ACAT, ↓ formation of cholesterol esters and limiting the transport of cholesterol in the blood. Naringin inhibits the oxidation of LDL-C, initiates AMPK, and has shown scavenging activity; ↑ the fecal excretion of cholesterol, ↓ the intestinal absorption, and ↑ turnover and excretion of bile acids (37,38).

Possibile azione anche su glicemia, pressione arteriosa, infiammazione e stress ossidativo

CONCLUSIONS

Statin discontinuation due to exaggerated toxicity-related concerns is a significant problem worldwide and appears to be growing. Statin discontinuation as a consequence of statin intolerance is associated with a significantly increased risk of CV morbidity and mortality (13). Nutraceuticals can be natural alternatives and support to pharmacological therapies in statin-intolerant patients, because they might significantly reduce LDL-C; exert other non-lipid-lowering properties, including reduction of other parameters of lipid profile, glucose, blood pressure, inflammation, and oxidative stress; and improve FMD and PWV. Equally important, despite still insufficient data, is that therapy with nutraceuticals seems to be very safe and well tolerated. However, further studies

TABLE 12 Which Nutraceuticals Can be Useful in Statin Intolerance, and for Which Patients

Recommendations	Class	Level
In high-risk or very-high-risk patients with complete statin intolerance who have not reached LDL-C targets with nonstatin therapy, nutraceuticals in monotherapy and combination should be considered.	Ila	B
In high-risk or very-high-risk patients with partial statin intolerance who have not reached LDL-C targets with tolerable statin therapy and/or nonstatin therapy, nutraceuticals in monotherapy and combination should be considered.	Ila	B
In individuals with statin intolerance and high cholesterol levels (and other risk factors) with intermediate CV risk who have not reached LDL-C targets, nutraceuticals in monotherapy and combination should be considered.	Ila	A

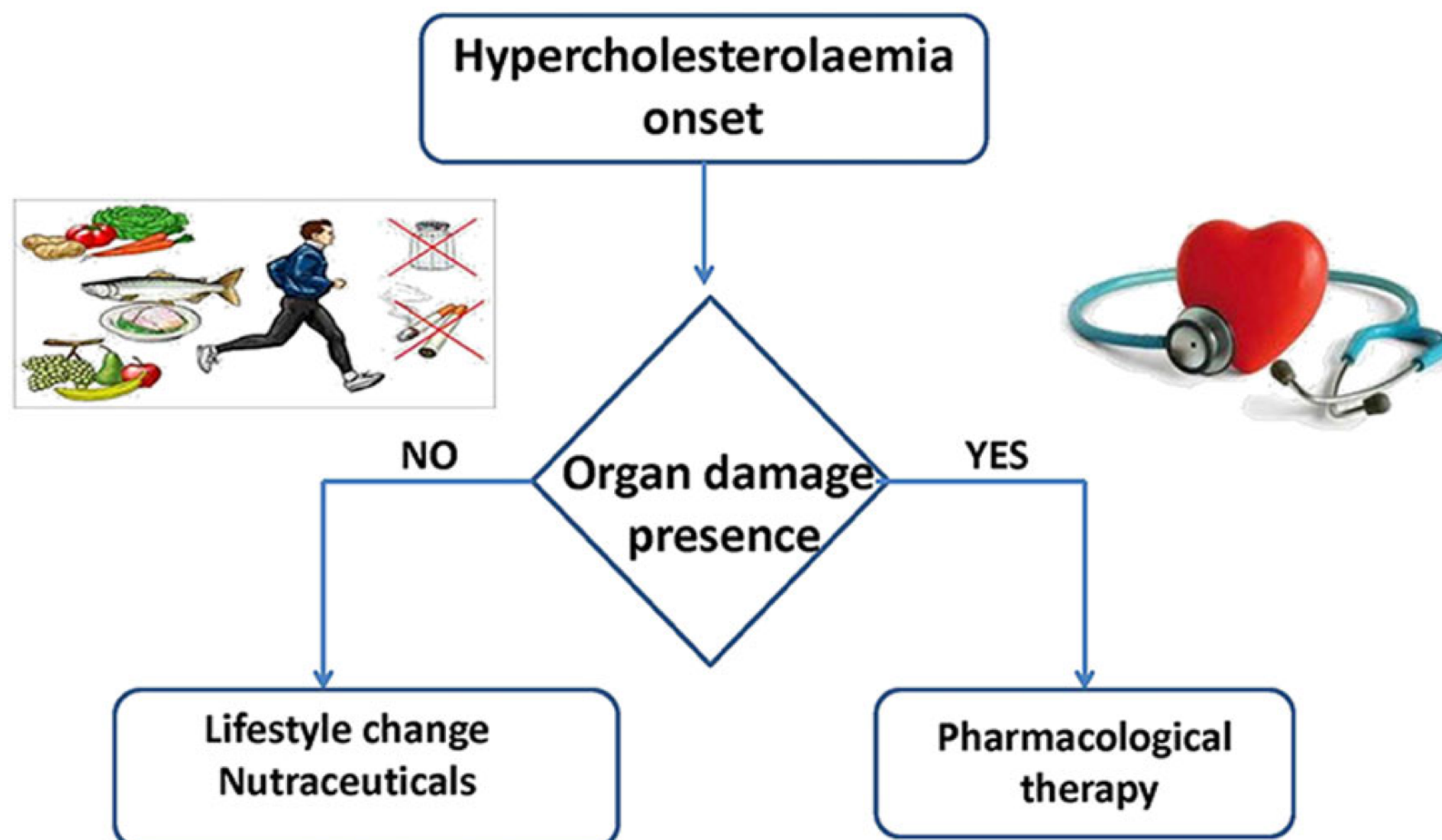
I nutraceutici nell'ipercolesterolemia

Opzione altamente desiderata nell'ipercolesterolemia lieve e moderata
Strumenti potenti per combattere questo problema di salute

REVIEW ARTICLE

Nutraceuticals in hypercholesterolaemia: an overview

proach to their health condition. In mild and moderate hypercholesterolaemia, a nutraceutical preventive approach would be a highly desired option.



jects. Further studies are needed to completely assess the potential of nutraceuticals for the prevention and treatment of hypercholesterolaemia, but they represent powerful tools to be taken into account to combat this health issue, which is considered among the highest of health risk factors.

Nutraceutici e ottimizzazione della terapia ipolipemizzante in pazienti ad alto rischio con dislipidemia

La dose e la composizione del nutraceutico devono essere controllate con cura

NONSTATIN DRUGS (M. VRABLIK, SECTION EDITOR)

The Role of Nutraceuticals in the Optimization of Lipid-Lowering Therapy in High-Risk Patients with Dyslipidaemia

Peter E. Penson^{1,2,3} • Maciej Banach^{4,5,6}

Accepted: 10 September 2020 / Published online: 18 September 2020

in the management of patients at high risk of ASCVD. In fact, there are five clear roles which nutraceuticals can play:

- 1) Managing residual risk associated with lipids other than LDL-C
- 2) Managing non-lipid-mediated residual risk
- 3) Optimizing LDL-C treatment in statin intolerance
- 4) Optimizing LCL-C treatment when add-on therapies for statins are not available
- 5) Adjuncts to lifestyle for individuals at high lifetime risk of ASCVD

risk reduction in REDUCE-IT is instructive. Clearly, the dose and composition of nutraceuticals must be as carefully controlled as is the case for conventional pharmaceuticals—and

Fitosteroli e MCV

Current Atherosclerosis Reports (2021) 23: 68
<https://doi.org/10.1007/s11883-021-00964-x>

CARDIOVASCULAR DISEASE AND STROKE (J. A. UNDERBERG AND J. NEWMAN,
SECTION EDITORS)

Phytosterols and Cardiovascular Disease

Umidakhon Makhmudova¹ · P. Christian Schulze¹ · Dieter Lütjohann² · Oliver Weingärtner¹ 

Abstract

Purpose of Review Coronary heart disease is the leading cause of mortality worldwide. Elevated blood cholesterol levels are not only the major but also the best modifiable cardiovascular risk factor. Lifestyle modifications which include a healthy diet are the cornerstone of lipid-lowering therapy. So-called functional foods supplemented with plant sterols lower blood cholesterol levels by about 10–15%.

Recent Findings In the recent revision of the ESC/EAS dyslipidemia guideline 2019, plant sterols are recommended for the first time as an adjunct to lifestyle modification to lower blood cholesterol levels. However, the German Cardiac Society (DGK) is more critical of food supplementation with plant sterols and calls for randomized controlled trials investigating hard cardiovascular outcomes. An increasing body of evidence suggests that plant sterols per se are atherogenic.

I fitosteroli riducono i livelli di colesterolo plasmatico del 10-15%

Dati sempre più convincenti suggeriscono che i fitosteroli siano di per sé aterogeni

Fitosteroli e sicurezza

Safety Concerns Beyond the Cardiovascular System

Besides proatherogenic effects, there are other safety concerns regarding phytosterols. As early as 2000, Ratnayake and colleagues found that vegetable oil rich in phytosterols makes red blood cells more rigid and less flexible and results in significant shortening of the lifespan of rats [59]. This finding leads to the ban of any phytosterol-enriched foods in Canada in 2003 [60].

Another concern coming from in vivo studies is the negative impact of phytosterols on hormonal status and the reproductive system of male and female rats [61, 62] and goldfish

Globuli rossi più rigidi e meno flessibili

Impatto negativo sulla situazione ormonale

Possibile interferenza sull'assorbimento di vitamine liposolubili -> suppl. con beta-carotene, se uso di fitosteroli a lungo termine

Further, there is concern that phytosterols can interfere with the absorption of several fat-soluble vitamins — such as tocoferol and β -carotene [64, 65]. The Scientific Committee on Food of the European Commission has significant safety issues and recommends the use of natural sources of β -carotene to compensate for the reduction of β -carotenes caused by long-term consumption of phytosterol-enriched foods [66].

Effetti della BPF su LDL: studio clinico

Advances in Biological Chemistry, 2014, 4, 129-137
 Published Online April 2014 in SciRes. <http://www.scirp.org/journal/abc>
<http://dx.doi.org/10.4236/abc.2014.42017>



The Effect of Bergamot-Derived Polyphenolic Fraction on LDL Small Dense Particles and Non Alcoholic Fatty Liver Disease in Patients with Metabolic Syndrome

Micaela Gliozzi¹, Cristina Carresi¹, Vincenzo Musolino¹, Ernesto Palma¹, Carolina Muscoli¹, Cristiana Vitale², Santo Gratteri¹, Giuseppe Muscianisi¹, Elzbieta Janda¹, Saverio Muscoli³, Francesco Romeo³, Salvatore Ragusa¹, Rocco Mollace¹, Ross Walker¹, James Ehrlich¹, Vincenzo Mollace^{1*}

Total Cholesterol (mg/dL)	245 ± 8.3	182 ± 7.1*
LDL-C (mg/mL)	162 ± 4.3	101 ± 1.8*
HDL-C (mg/mL)	38 ± 3.8	49 ± 4*
Triglycerides (mg/mL)	232 ± 5.1	160 ± 4.8*

Plasma lipoprotein plasma diameter, nm	Baseline	BPF
VLDL	55.3 ± 6.4	44.5 ± 5.2*
LDL	22.6 ± 1.7	18.0 ± 0.8*
HDL	7.5 ± 0.8	9.6 ± 0.9*
Plasma lipoprotein particles, nmol/L		
Total VLDL	83 ± 14	54 ± 12*
Large VLDL	4.2 ± 2	1.8 ± 1.3*
Medium VLDL	31 ± 9	14 ± 8*
Small VLDL	43 ± 9	38 ± 10
Total LDL	1477 ± 75	1293 ± 101*
IDL	77 ± 16	38 ± 10*
Large LDL	424 ± 87	653 ± 95*
Small LDL	986 ± 105	612 ± 98*
Total HDL	30 ± 2	36 ± 3*
Large HDL	5 ± 3	15 ± 4*
Medium HDL	7 ± 4	7 ± 3
Small HDL	18 ± 5	14 ± 4*

La BPF migliora significativamente il profilo lipidico nei 107 pazienti in studio

Applicazioni cliniche del bergamotto per la riduzione del colesterolo elevato

Published in final edited form as:

Integr Food Nutr Metab. 2019 March ; 6(2): . doi:10.15761/IFNM.1000249.

Clinical application of bergamot (*Citrus bergamia*) for reducing high cholesterol and cardiovascular disease markers

Mirielle C. Nauman and Jeremy J. Johnson

University of Illinois at Chicago, College of Pharmacy, Department of Pharmacy Practice

quantified prior to bergamot and at the completion of the study. Three of the studies suggested an increase in HDL by up to 4 mg/dl (Table 1). This is significant because HDL is often difficult to increase apart from lifestyle changes. Regarding the mechanism of action

Conclusion

The results of five different clinical trials (Table 1) using bergamot in various forms suggest the polyphenol fraction can lower LDL-C and total cholesterol. Several studies suggested that bergamot polyphenols can reduce triglycerides and increase HDL-C, however, the

proposed mechanism of action. Taken together, these early clinical trials along with the mechanistic studies that have been performed suggest that bergamot can reduce total cholesterol and LDL-C through mechanisms that are distinct from current pharmaceutical approaches.

- **5 studi clinici indicano che la BPF riduce colesterolo totale e LDL (e TG)**
- **Si è osservato un aumento delle HDL fino a 4 mg/dl -> risultato molto importante (HDL molto difficile da aumentare)**
- **I meccanismi di riduzione del colesterolo sono diversi da quelli dei farmaci**

Meccanismo ipocolesterolemizzante del bergamotto



Article Defining the Cholesterol Lowering Mechanism of Bergamot (*Citrus bergamia*) Extract in HepG2 and Caco-2 Cells

Yunying Huang^{1,2}, Restituto Tocmo¹ , Mirielle C. Nauman¹ , Monica A. Haughan^{1,3} and Jeremy J. Johnson^{1,*}

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5. Conclusions

In conclusion, BFE and its principal constituents reduce cholesterol in a mechanism that is distinct from direct inhibition of HMG-CoA reductase, as has been suggested previous laboratory and clinical studies. This is significant as there is now evidence that bergamot fruit extract does not share the same pharmacological mechanism as the cholesterol-lowering drugs known as statins. Our results provide new insights into the molecular mechanism of the cholesterol-lowering effects of BFE. The cholesterol-lowering effect of BFE appears to be mediated through several mechanisms, including cholesterol biosynthesis in HepG2 cells and cholesterol cellular transport in Caco-2 cells. Overall, the data support the hypothesis that BFE and its principal constituents can alter cholesterol synthesis and uptake. Further studies will be focus on further evaluating these findings in

metabolism. BFE may represent a potential alternative therapeutic approach for lowering cholesterol, especially in subjects suffering from statin intolerance. These findings shed light on the use of BFE in reduction of overall cardiovascular disease risk.

- **Gli estratti dal bergamotto non condividono il meccanismo d'azione delle statine**
- **Meccanismi molecolari di BPF -> alterazione della biosintesi e del trasporto del colesterolo**
- **Gli estratti dal bergamotto rappresentano un'alternativa terapeutica per abbassare i livelli di colesterolo, soprattutto in soggetti che non tollerano le statine**

Posizione dell'ACC su ruolo dei nutraceutici in pazienti intolleranti alle statine

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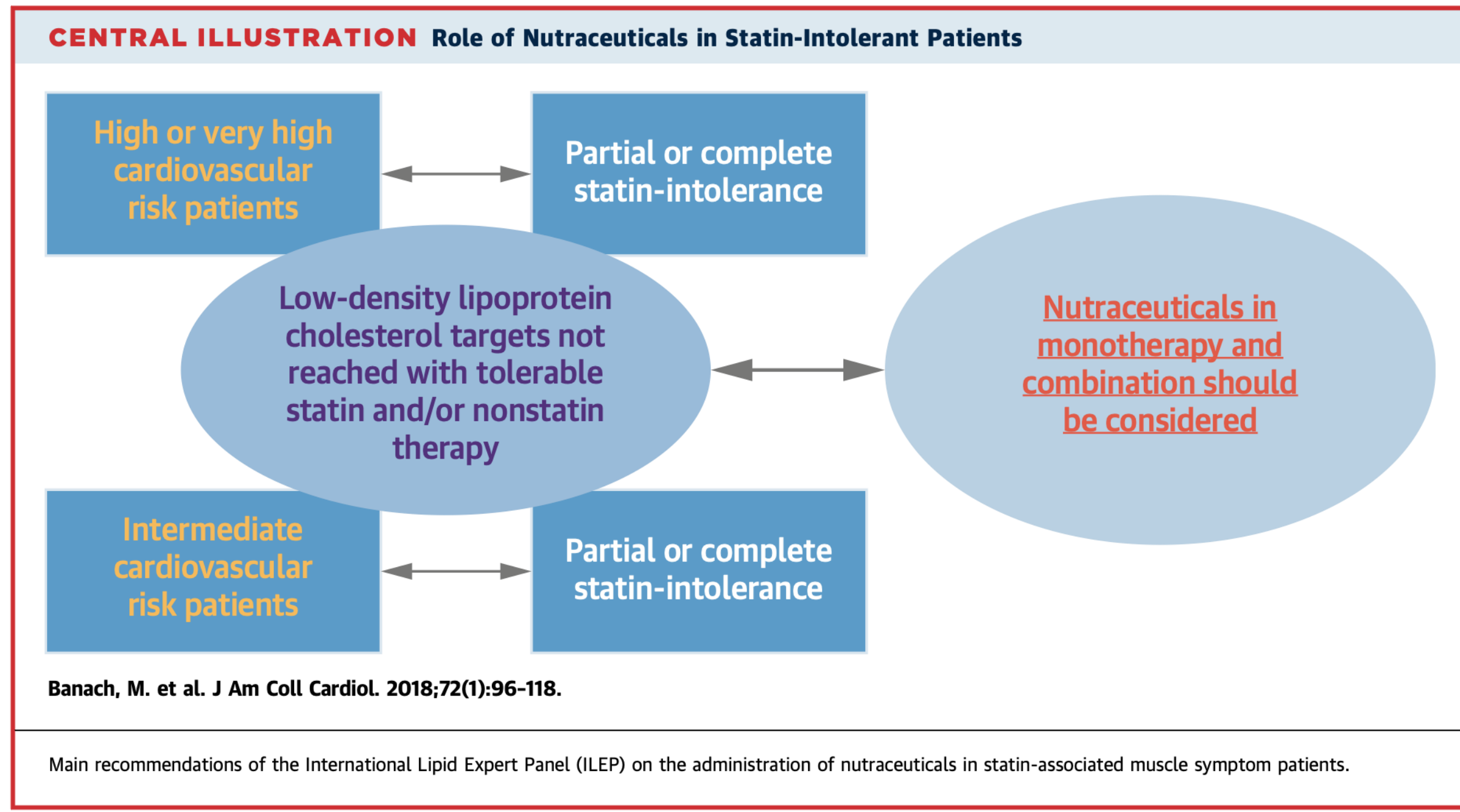
VOL. 72, NO. 1, 2018

JACC STATE-OF-THE-ART REVIEW

The Role of Nutraceuticals in Statin Intolerant Patients



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Bergamot	Ila	B	<p>HMGR inhibits HMG-CoA reductase and ACAT, ↓ formation of cholesterol esters and limiting the transport of cholesterol in the blood. Naringin inhibits the oxidation of LDL-C, initiates AMPK, and has shown scavenging activity; ↑ the fecal excretion of cholesterol, ↓ the intestinal absorption, and ↑ turnover and excretion of bile acids (37,38).</p>
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Ruolo riconosciuto degli estratti di Bergamotto

Attività ipocolesterolemizzante dell'acido ellagico

BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY
2019, VOL. 83, NO. 5, 952–959
<https://doi.org/10.1080/09168451.2019.1576498>



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Ellagic acid affects mRNA expression levels of genes that regulate cholesterol metabolism in HepG2 cells

Shizuka Kubota, Yuma Tanaka and Satoshi Nagaoka

Department of Applied Life Science, Faculty of Applied Biological Sciences, Gifu University, Gifu, Japan

ABSTRACT

Ellagic acid has been shown to improve cholesterol metabolism in animal studies, but the molecular mechanisms underlying this function have not been fully understood. We performed DNA microarray analysis to elucidate the effects of ellagic acid on cholesterol metabolism in HepG2 hepatocytes. This revealed that the expression levels of several genes related to cholesterol metabolism, including the low-density lipoprotein receptor (LDLR), were changed by ellagic acid treatment. Using a real-time PCR and immunoblot we confirmed that ellagic acid treatment up-regulated mRNA and protein expression level of the LDLR. Moreover, in the presence of 25 μ M ellagic acid, extracellular apoB protein and MTP mRNA levels were significantly decreased. These findings indicate that ellagic acid improves cholesterol metabolism through the up-regulation of LDLR, down-regulation of MTP mRNA and reduces extracellular apoB levels. The ellagic acid-induced up-regulation of LDLR occurred via the extracellular signal-regulated kinase (ERK) signaling pathway in HepG2 hepatocytes.

In conclusion, the present study indicates that ellagic acid improves cholesterol metabolism through up-regulation of LDL receptor. Moreover, ellagic acid decreased MTP mRNA and extracellular apoB levels. The importance of hepatic LDLRs in systemic cholesterol excretion is exemplified by patients suffering from familial hypercholesterolemia, an autosomal dominant disorder whereby one or both LDLR alleles do not encode functional receptors [38]. Therefore, the up-regulation of LDLR protein and mRNA induced by ellagic acid may contribute to the cholesterol-lowering effect of ellagic acid.

Meccanismo d'azione -> *up-regulation* (=aumento della densità) del recettore per le LDL e riduzione dei livelli di ApoB extra-cellulare

Article

Unripe *Rubus coreanus* Miquel Extract Containing Ellagic Acid Regulates AMPK, SREBP-2, HMGCR, and INSIG-1 Signaling and Cholesterol Metabolism In Vitro and In Vivo

Ki Hoon Lee, Eui-Seon Jeong, Goeun Jang, Ju-Ryun Na, Soyi Park, Wan Seok Kang, Eun Kim, Hakjoon Choi, Jin Seok Kim and Sunoh Kim * 

5. Conclusions

In conclusion, our results suggested that 5-*u*RCK and ellagic acid had hypolipidemic effects in an HCD-induced hypercholesterolemic rat model. Our in vitro and in vivo findings provide evidence that 5-*u*RCK and ellagic acid provide advanced protection against HCD-related lipid accumulation and liver dysfunction and may be more effective functional treatments for managing hypercholesterolemia.

RESEARCH

Open Access



The cholesterol-lowering effect of unripe *Rubus coreanus* is associated with decreased oxidized LDL and apolipoprotein B levels in subjects with borderline-high cholesterol levels: a randomized controlled trial

Jung Min Cho^{1,2}, Jisuk Chae^{1,2}, Sa Rang Jeong^{1,2}, Min Jung Moon^{1,2}, Ki-Chan Ha³, Sunoh Kim^{4*} and Jong Ho Lee^{1,2*}



Fig. 2 Comparison of the change values of total cholesterol, LDL-cholesterol, non-HDL-cholesterol and apolipoprotein B levels between the placebo (■) group and the uRC (□) group before and after supplementation of uRC. * $P < 0.05$ and ** $P < 0.01$ derived from independent t-test. A two-tailed P -value of less than 0.05 was considered statistically significant. Δ (delta, change) values were calculated as the difference from the baseline (0-week). Data are presented as means Mean \pm SE

Esperidina e azione sui fattori di rischio CV



Review

Effect of Hesperidin on Cardiovascular Disease Risk Factors: The Role of Intestinal Microbiota on Hesperidin Bioavailability

Anna Mas-Capdevila ^{1,2,†}, Joan Teichenne ^{1,†}, Cristina Domenech-Coca ^{1,†}, Antoni Caimari ^{1,3}, Josep M Del Bas ¹, Xavier Escoté ^{1,2,*}  and Anna Crescenti ^{1,*}

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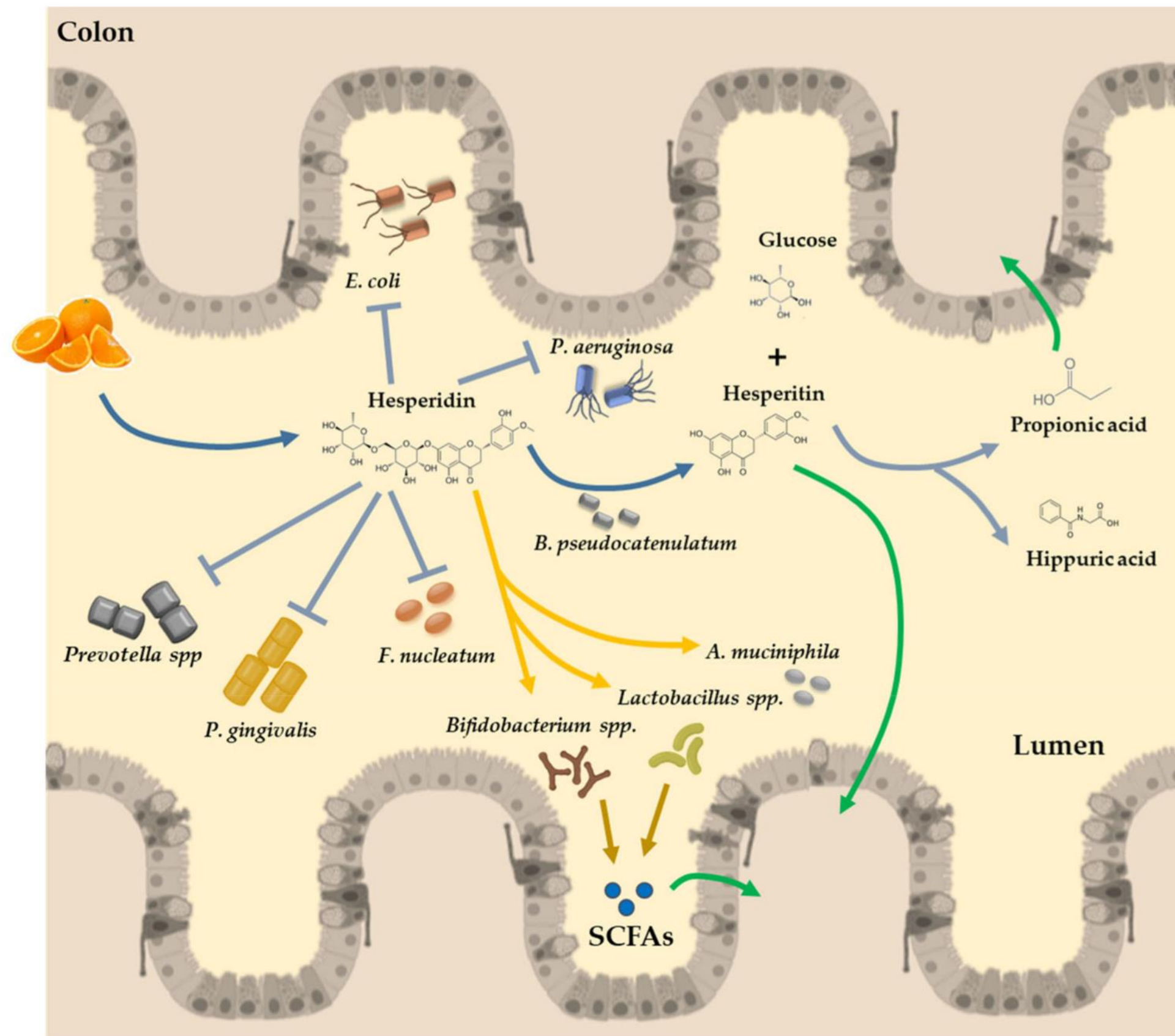
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Esperidina -> riduzione del colesterolo plasmatico ed epatico, attraverso una down-regulation (=riduzione della sintesi) dell'attività dell'enzima HMG-CoA reduttasi e ACAT

triglycerides [43]. Furthermore, it was also demonstrated that hesperidin administration led to a decrease in plasma and hepatic cholesterol levels through a downregulation of the hepatic 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase and acyl CoA: cholesterol acyltransferase (ACAT) activities [43]. Wu et al. demonstrated similar lipid-regulating effects with neohesperidin.

Oltre la gestione della dislipidemia: fisiopatologia della MetS

Ruolo chiave dell'infiammazione e dell'insulino-resistenza

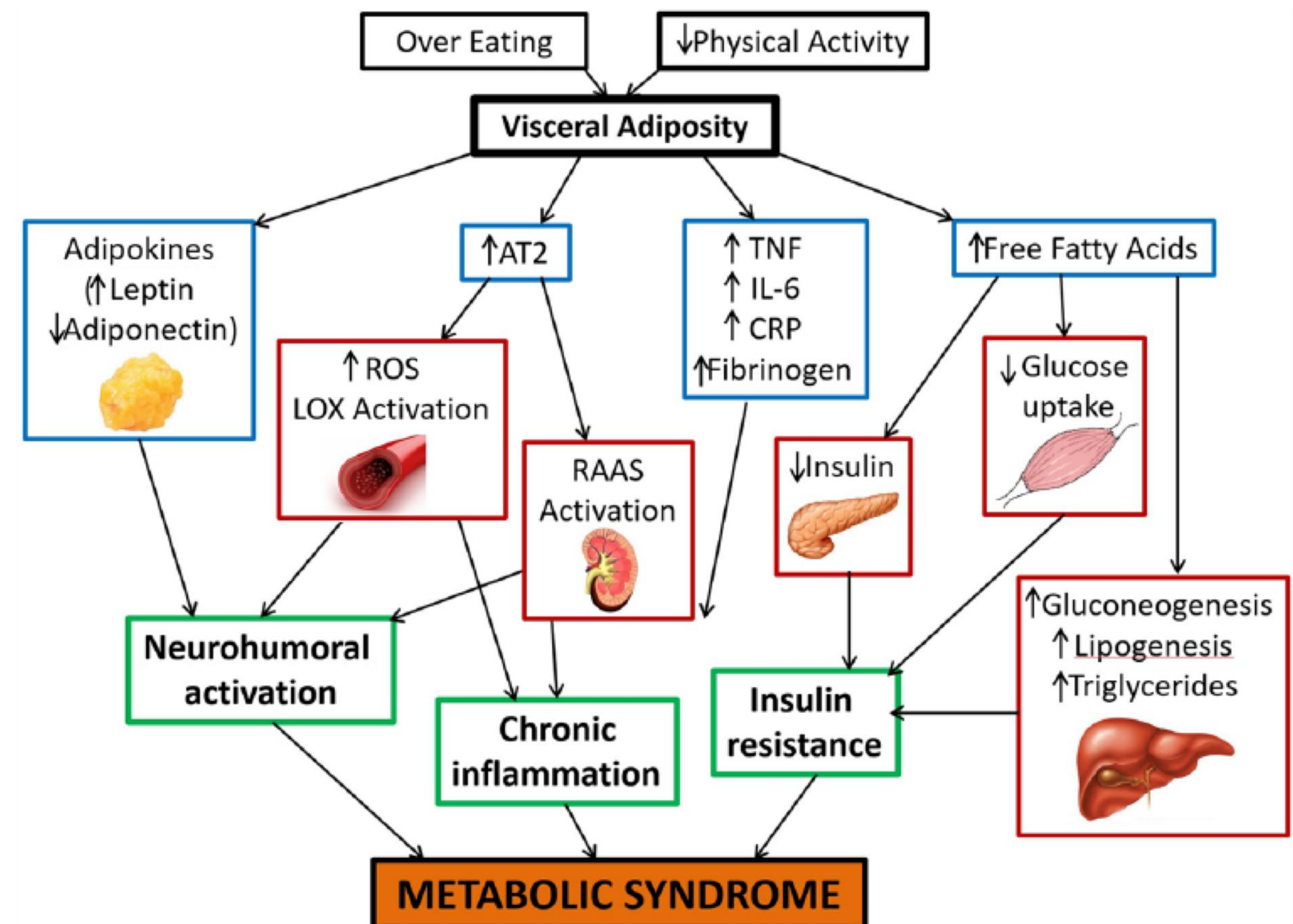
I nutraceutici sono altamente promettenti come strumenti terapeutici

Metabolic syndrome: pathophysiology, management, and modulation by natural compounds

Yogita Rochlani, Naga Venkata Pothineni, Swathi Kovelamudi and Jawahar L. Mehta

Ther Adv Cardiovasc Dis
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1753944717711379
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ance. In this context, the development of nutraceuticals that are readily available and with minimal side effects may represent an area of promise in the development of novel therapies.



MetS come un insieme di disregolazioni metaboliche (insulino-resistenza, dislipidemia aterogena, obesità centrale e ipertensione)



International Journal of
Molecular Sciences

Review

Metabolic Syndrome: Updates on Pathophysiology and Management in 2021

Abstract: Metabolic syndrome (MetS) forms a cluster of metabolic dysregulations including insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension. The pathogenesis of MetS encompasses multiple genetic and acquired entities that fall under the umbrella of insulin resistance and chronic low-grade inflammation. If left untreated, MetS is significantly associated with an increased risk of developing diabetes and cardiovascular diseases (CVDs). Given that CVDs constitute by far the leading cause of morbidity and mortality worldwide, it has become essential to investigate the role played by MetS in this context to reduce the heavy burden of the disease. As such, and while MetS relatively constitutes a novel clinical entity, the extent of research about the disease has been exponentially growing in the past few decades. However, many aspects of this clinical entity are still not completely understood, and many questions remain unanswered to date. In this

- **La MetS è associata a un aumentato rischio di sviluppo di diabete e MCV**
- **Gli sforzi terapeutici si devono concentrare sull'eccesso di adipe e sull'insulino-resistenza**
- **Co-morbidity associate a MetS: NAFLD, malattia microvascolare...**

4. Conclusions

A cluster of components or risk factors are associated with an increased risk of CVDs and T2DM, and MetS has a prevalence that has been on the rise across all ages. While it is not clear if MetS can be treated in and of itself, ongoing research seems to be unlocking different targets along the disease's pathway. Concentrating therapeutic efforts on treating the excess adiposity and insulin resistance associated with the MetS may provide the most overall success in attaining these goals. Much has been answered in the past few years, but much remains to be unraveled. The associations of MetS with other comorbidities such as NAFLD, sleep disorders, reproductive tract disorders, and microvascular disease are examples of areas yet to be fully determined.

Definizione del problema e contesto clinico

Insulino-resistenza: condizione che si viene a creare quando le cellule dell'organismo presentano una scarsa sensibilità all'insulina (per carenza numerica o funzionale dei recettori per l'insulina presenti sulla superficie delle cellule); pertanto, il glucosio non riesce ad essere assorbito dalle cellule stesse in risposta all'azione esercitata dall'ormone e rimane nel torrente circolatorio. Questa condizione predispone a diabete e a MCV.

Come si valuta: tramite l'HOMA Test, comparando le concentrazioni del glucosio e di insulina nel plasma a digiuno; $HOMA\ Index = (glicemia \times insulinemia) / 405$ (V.N.: 0.23-2.5).

Fisiopatologia dell'insulino-resistenza in menopausa (1)



Review

Menopause-Associated Lipid Metabolic Disorders and Foods Beneficial for Postmenopausal Women

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I disordini del metabolismo lipidico associati alla menopausa portano
allo sviluppo di insulino-resistenza

Fisiopatologia dell'insulino-resistenza in menopausa (2)

Abstract: Menopause is clinically diagnosed as a condition when a woman has not menstruated for one year. During the menopausal transition period, there is an emergence of various lipid metabolic disorders due to hormonal changes, such as decreased levels of estrogens and increased levels of circulating androgens; these may lead to the development of metabolic syndromes including cardiovascular diseases and type 2 diabetes. Dysregulation of lipid metabolism affects the body fat mass, fat-free mass, fatty acid metabolism, and various aspects of energy metabolism, such as basal metabolic ratio, adiposity, and obesity. Moreover, menopause is also associated with alterations in the levels of various lipids circulating in the blood, such as lipoproteins, apolipoproteins, low-density lipoproteins (LDLs), high-density lipoproteins (HDL) and triacylglycerol (TG). Alterations in lipid metabolism and excessive adipose tissue play a key role in the synthesis of excess fatty acids, adipocytokines, proinflammatory cytokines, and reactive oxygen species, which cause lipid peroxidation and result in the development of insulin resistance, abdominal adiposity, and dyslipidemia. This review discusses dietary recommendations and beneficial compounds, such as

Periodo di transizione menopausale -> cambiamenti ormonali (riduzione dei livelli di estrogeni e aumento dei livelli di androgeni) -> alterazioni del metabolismo lipidico (LDL, HDL e TG)-> alterazioni della massa grassa e magra e del metabolismo degli acidi grassi -> adiposità viscerale -> sintesi citochine infiammatorie -> insulino-resistenza -> sindrome metabolica -> T2D e MCV

Cont.

Livelli di E2 inversamente
proporzionali ai livelli di TC, LDL-C TG

Livelli più alti di FAI (Free Androgen
Index) sono associati a TC, LDL-C, TG
più alti e HDL più bassi

to indicate excess body fat [66]. A well-documented metabolic phenotypic feature observed after menopause is an increased tendency for body fat deposition in the abdominal region with greater waist circumference [43]. The rapid decline in ovarian function and the subsequent decline in the production of circulating steroid-based sex hormones—such as estrogen—associated with menopause results in increased overall adiposity, especially the abdominal visceral adiposity [67,68]. Increased adiposity in postmenopausal women is significantly associated with hyperinsulinemia, which suggests that insulin resistance may be responsible for the development of the key features of postmenopausal dyslipidemia [69], obesity [70], metabolic syndrome [71], and type 2 diabetes [72].

that the alterations in various body fats were related to the changes in the menopausal status and concentrations of E2 and follicle-stimulating hormone (FSH). The alterations in various fats were initiated during the late phases of menopause. The levels of total cholesterol, LDL, triglycerides, and lipoprotein peaked during menopausal transition and the early postmenopausal stage [22,25]. The SWAN study also reported that the middle-aged women with the highest quartile E2 levels had the lowest levels of total cholesterol and LDL, whereas women with the lowest quartile FSH levels had the highest levels of total cholesterol and LDL-C. Lower levels of E2 and sex hormone-binding globulin were associated with medium to low LDL concentrations, while higher levels of FAI (free androgen index) were associated with higher cholesterol, TG, and LDL levels and lower HDL levels in middle-aged premenopausal women [56]. The changes in sex hormone levels and lipid metabolism

Menopausa -> tendenza alla
formazione di grasso a livello
addominale (e viscerale)

Aumentata adiposità
postmenopausale -> associata a
insulino-resistenza

Cont.

One of the major reasons for increased obesity among menopausal women is the decreased level of estrogens. Obesity is associated with a higher probability of surgical menopause, where the ovaries are surgically removed by bilateral oophorectomy [2]. Clegg et al. demonstrated that the absence of estrogens may be an important obesity-triggering factor [90]. Moreover, some studies have reported that estrogen deficiency enhances metabolic dysfunction and predisposes the individual to type 2 diabetes, metabolic syndrome, and CVD [16]. Aromatase (estrogen synthase) knockout mice—that cannot synthesize E2—are obese and insulin-resistant [91]. As described previously, ER α appears to be a key regulator of obesity because ER α knockout mice exhibit increased obesity and glucose intolerance compared with wild-type female mice [77,92]. A recent study reported that postmenopausal women who have received aromatase inhibitors for the treatment of breast cancer exhibited higher body fat percentage and insulin resistance than control subjects without a history of breast cancer [93].

Assenza di estrogeni -> fattore *trigger* per obesità

Donne in post-menopausa che assumono inibitori dell'aromatasi per tumore mammella -> più alta % di grasso corporeo e insulino-resistenza

Women in midlife exhibit continuous weight gain. However, the reasons for increased obesity among menopausal women are not fully understood and are contradictory. There are several

Cont.

Donne in post-menopausa -> riduzione di consumi energetici, forse da riduzione di attività fisica -> perdita di massa magra -> riduzione del metabolismo energetico basale

A reduction in energy expenditure during midlife can also cause obesity during menopause. According to a four-year follow-up study, women undergoing menopause exhibited a greater decrease in energy expenditure than premenopausal women [94], which may be attributed to the reduction in physical activity. The loss of LBM leads to a reduction in basal energy metabolism with aging [95]. A

Quali trattamenti: dieta, esercizio fisico o nutraceutici?

Dieta e altri rimedi:

- Aumentare l'attività fisica
- Perdere peso
- Migliorare qualità alimentazione
- Migliorare qualità e quantità del sonno
- Ridurre lo stress
- Digiuno intermittente
- Nutraceutici

Ruolo della dieta

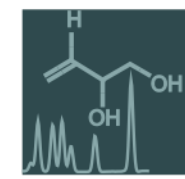
Dieta sana -> effetto protettivo significativo contro lo sviluppo dell'insulino-resistenza rispetto a "dieta occidentale"

Dieta sana -> basso livello di calorie, CHO e grassi saturi

Dieta sana -> effetti protettivi verso livelli di PA e TG (transizione menopausale), HDL-C e obesità (donne in post-menopausa)

against the dysregulation of lipid metabolism (lower TG and higher HDL-C). A healthy diet exhibits a significant protective effect against metabolic syndrome among postmenopausal women relative to that of a Western diet, which is unbalanced and has high energy, and abundant carbohydrates and saturated fats (OR (95% CI) for highest vs. lowest quartile = 0.60 (0.41–0.86); p for trend = 0.004). Additionally, a healthy diet exerts protective effects against blood pressure and TG levels—during menopausal transition—and obesity and HDL-C among postmenopausal women [107].

Ruolo dell'attività fisica (AF)



metabolites

Metabolites 2022, 12, 208.



Review

Potential Mechanisms for How Long-Term Physical Activity May Reduce Insulin Resistance

and fasting) IR, fat oxidation, and glucose tolerance [24–28]. Long-term PA may also improve body composition and promote many effects such as enhanced skeletal muscle mitochondria number and oxidative capacity, improve vascularization and cardiac output, reduce blood concentration of HbA1c and triglycerides, lower blood pressure, and reduce total and cardiovascular mortality [29–36]. Most of the available data do not allow a clear distinction between the effects of long-term PA per se, and the effects of weight loss on IR [37,38]. Although weight loss due to either dietary energy restriction or long-term PA may both reduce IR, greater effects are seen after PA-induced weight loss [37,38]. The greatest effect

AF a lungo termine -> miglioramento della composizione corporea, aumento del numero e capacità ossidativa dei mitocondri muscolari

Perdita di peso -> riduzione di IR, ma effetti maggiori si osservano dopo perdita di peso indotta da AF

Nutraceutici e MetS

Ruolo anti-ossidante e anti-infiammatorio di bergamotto e polifenoli
Azione insulino sensibilizzante, su PA e composizione corporea dei
polifenoli:

Bergamot essential oil

Anti-inflammatory and antioxidant effects
↓ Lectin-like oxidized low-density lipoprotein receptor-1 expression
↓ Reactive oxygen species formation

Polyphenols

Antithrombotic
Anti-inflammatory
↑ Insulin sensitivity
Improves fasting blood glucose, blood pressure, and body composition

Bergamot orange (*Citrus bergamia*)
Active ingredient: bergamot essential oil

Anticancer–anti-inflammatory–antimicrobial–antioxidant–antianxiety properties—↓ ROS formation—↓ lectin-like LDL receptor-1 expression [208]

Naringina: non solo azione ipolipemizzante


International Journal for Vitamin and Nutrition Research → Advance Articles |

Naringin reduces body weight, plasma lipids and increases adiponectin levels in patients with dyslipidemia

Jessica Lucia Barajas-Vega, Abdel Kerim Raffoul-Orozco ✉, Diego Hernandez-Molina, Ana Elisa Ávila-González, Teresa Arcelia García-Cobian, Edy David Rubio-Arellano, and Ernesto Javier Ramirez-Lizardo

Published Online: 9 Jun 2020 • Doi: <https://doi.org/10.1024/0300-9831/a000658>

 Tools

 Share

Abstract

Abstract. Naringin is a citrus-flavonoid which has been shown to have positive metabolic and anti-inflammatory effects. For this reason, we believe it would be interesting to study the effects of Naringin administration on body weight, BMI, lipid profile and adiponectin levels in patients with dyslipidemia, especially considering that dyslipidemias along with obesity and subsequent cardiometabolic complications are some of the most important public health issues plaguing our society today. A double-blind, randomized clinical trial was conducted in a group of 28 adult patients previously diagnosed with dyslipidemia who attended the Institute of Experimental and Clinical Therapeutics. Patients were divided into two groups; the first group (n = 14) received 450 mg of naringin every 24 hours, in the mornings, while the second group (n = 14) was given a homologated placebo over the course of a 90-day period. Significant differences were observed in naringin group compared to the placebo group in terms of decreased BMI (30.6 ± 3.19 vs 33.3 ± 3.23 kg/m²; p = 0.03), total cholesterol (182 ± 20.2 vs 245 ± 24.1 mg/dl; p < 0.01), LDL cholesterol (100 ± 17.5 vs 125 ± 38.3 mg/dl; p = 0.03) and an increase in adiponectin levels (0.82 ± 0.25 vs 0.59 ± 0.19 µg/ml; p = 0.01). Our results support the use of Naringin as a potential therapeutic agent which could play an important role in the management of metabolic disorders.

Acido ellagico e insulino-resistenza

Kazemi et al. *J Ovarian Res* (2021) 14:100
<https://doi.org/10.1186/s13048-021-00849-2>

Journal of Ovarian Research

RESEARCH

Open Access



Randomized double blind clinical trial evaluating the Ellagic acid effects on insulin resistance, oxidative stress and sex hormones levels in women with polycystic ovarian syndrome

Conclusion

In conclusion, the results of this study indicated that 8 weeks of supplementation with EA, 200 mg/day, reduced the levels of blood sugar, blood lipids and IR in PCOS patients. Also, with the ameliorating in the status of oxidative stress and inflammatory status, at the end of the study, we saw a significant decrease in the amount of AMH in these patients. These results provide evidence to support the view that polyphenol antioxidant group with reducing the biochemical factors, can play an important role in helping to control the condition of this syndrome.

Acido ellagico e MetS

Article

Ellagic Acid Effect on the Components of Metabolic Syndrome, Insulin Sensitivity and Insulin Secretion: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Gladys Maribel Hidalgo-Lozada ¹, Angélica Villarruel-López ^{2,*}, Esperanza Martínez-Abundis ^{1,3}, Olga Vázquez-Paulino ², Manuel González-Ortiz ³ and Karina Griselda Pérez-Rubio ^{1,3,*}

RCT vs placebo in pazienti con MetS: acido ellagico, somministrato per 12 settimane, ha evidenziato un miglioramento delle componenti della MetS (pressione arteriosa, TG, glicemia e insulinemia a digiuno)

Si è evidenziato anche un aumento della sensibilità all'insulina

Abstract: Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors, usually with a common pathophysiological origin in insulin resistance and abdominal obesity. Considering the reported effects of ellagic acid (EA) on insulin resistance and abdominal obesity, the aim of this study was to evaluate the effect of EA on the components of MetS, insulin sensitivity and insulin secretion by conducting a randomized, double-blind, placebo-controlled, clinical trial with 32 volunteers diagnosed with MetS. Sixteen patients were randomly allocated, received 500 mg of EA orally twice a day for 12 weeks, and the other 16 received a placebo. Clinical and laboratory determinations were obtained at baseline and at the end of the study. After EA administration, patients reduced their waist circumference (females: 102.2 ± 4.2 to 99.5 ± 3.2 cm ($p < 0.05$); males: 99.8 ± 6.7 to 96.0 ± 4.7 cm ($p < 0.01$)), systolic blood pressure (118.1 ± 10.1 to 113.7 ± 7.8 mmHg ($p < 0.01$)), diastolic blood pressure (118.1 ± 10.1 to 113.7 ± 7.8 mmHg ($p < 0.01$)), triglycerides (2.8 ± 1.1 to 2.1 ± 0.7 mmol/L ($p < 0.01$)), fasting plasma glucose (6.5 ± 0.5 to 5.7 ± 0.6 mmol/L ($p < 0.01$)), fasting plasma insulin ($p < 0.01$), and insulin secretion ($p < 0.05$), with an increase of insulin sensitivity ($p < 0.01$). In male patients, high-density lipoprotein cholesterol increased ($p < 0.05$). In conclusion, EA improved the components of MetS, reduced hyperinsulinemia, and improved insulin sensitivity.

Esperidina e pressione arteriosa

European Journal of Nutrition (2021) 60:1277–1288

<https://doi.org/10.1007/s00394-020-02279-0>

ORIGINAL CONTRIBUTION

Effects of hesperidin in orange juice on blood and pulse pressures in mildly hypertensive individuals: a randomized controlled trial (Citrus study)

Conclusion Hesperidin in OJ reduces SBP and PP after sustained consumption, and after a single dose, the chronic consumption of EOJ enhances its postprandial effect. Decreases in systemic and transcriptomic biomarkers were concomitant with BP and PP changes. EOJ could be a useful co-adjuvant tool for BP and PP management in pre- and stage-1 hypertensive individuals.

Studio CITRUS (RCT)

Esperidina in pazienti con pre-ipertensione e con ipertensione stadio 1 ha dimostrato una riduzione di SBP e PP dose-dipendente

Perspectives

In a randomized, controlled clinical trial with pre- and stage-1 hypertensive individuals, we showed that sustained consumption of hesperidin promoted a dose-dependent decrease in SBP and PP with the hesperidin content of the beverage administered. Our data are the first to support an effect of dietary flavanones on human arterial stiffness. Additionally, we report for the first time the postprandial benefits of a hesperidin-enriched beverage to BP and PP, as well as the fact that its sustained consumption enhances these benefits. Regular consumption of OJ, particularly hesperidin-rich OJ, could be a useful co-adjuvant tool for BP management in pre- and stage-1 hypertensive individuals. This fact has public health implications in preventive medicine for reducing the secondary effects of long-term medical treatment of mild hypertension.

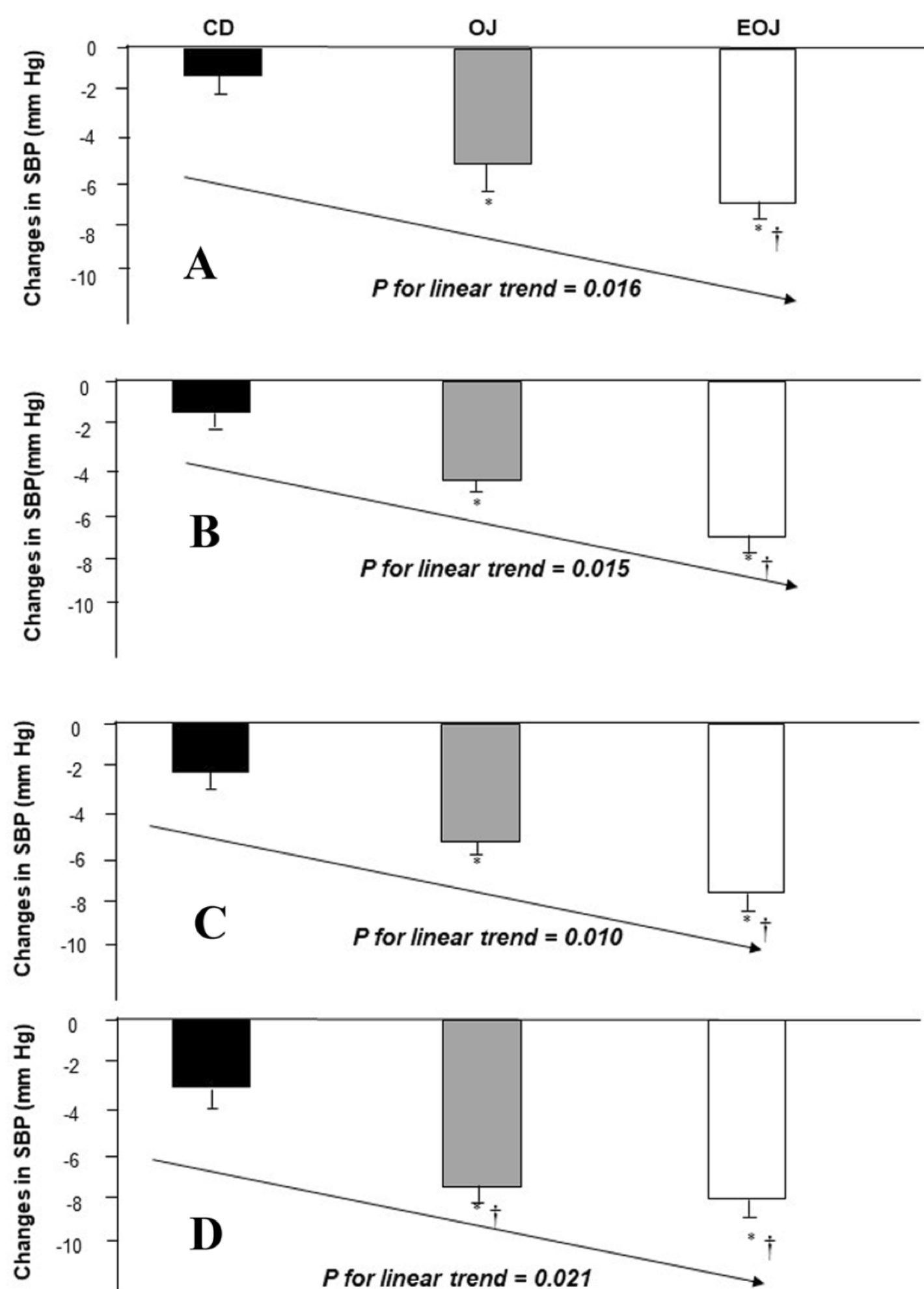


Fig. 3 Changes in systolic blood pressure (SBP) at 2 (a), 6 (b), 10 (c), and 12 (d) weeks after sustained consumption of control drink (CD), orange juice (OJ), and hesperidin-enriched OJ (EOJ). * $P < 0.05$ versus baseline; † $P < 0.05$ versus CD

Frazione polifenolica del bergamotto: azione oltre il miglioramento del profilo lipidico

Advances in Biological Chemistry, 2014, 4, 129-137
Published Online April 2014 in SciRes. <http://www.scirp.org/journal/abc>
<http://dx.doi.org/10.4236/abc.2014.42017>



Miglioramento del profilo lipidico

Miglioramento del profilo glicemico

Riduzione sostanziale del livello di steatosi epatica

The Effect of Bergamot-Derived Polyphenolic Fraction on LDL Small Dense Particles and Non Alcoholic Fatty Liver Disease in Patients with Metabolic Syndrome

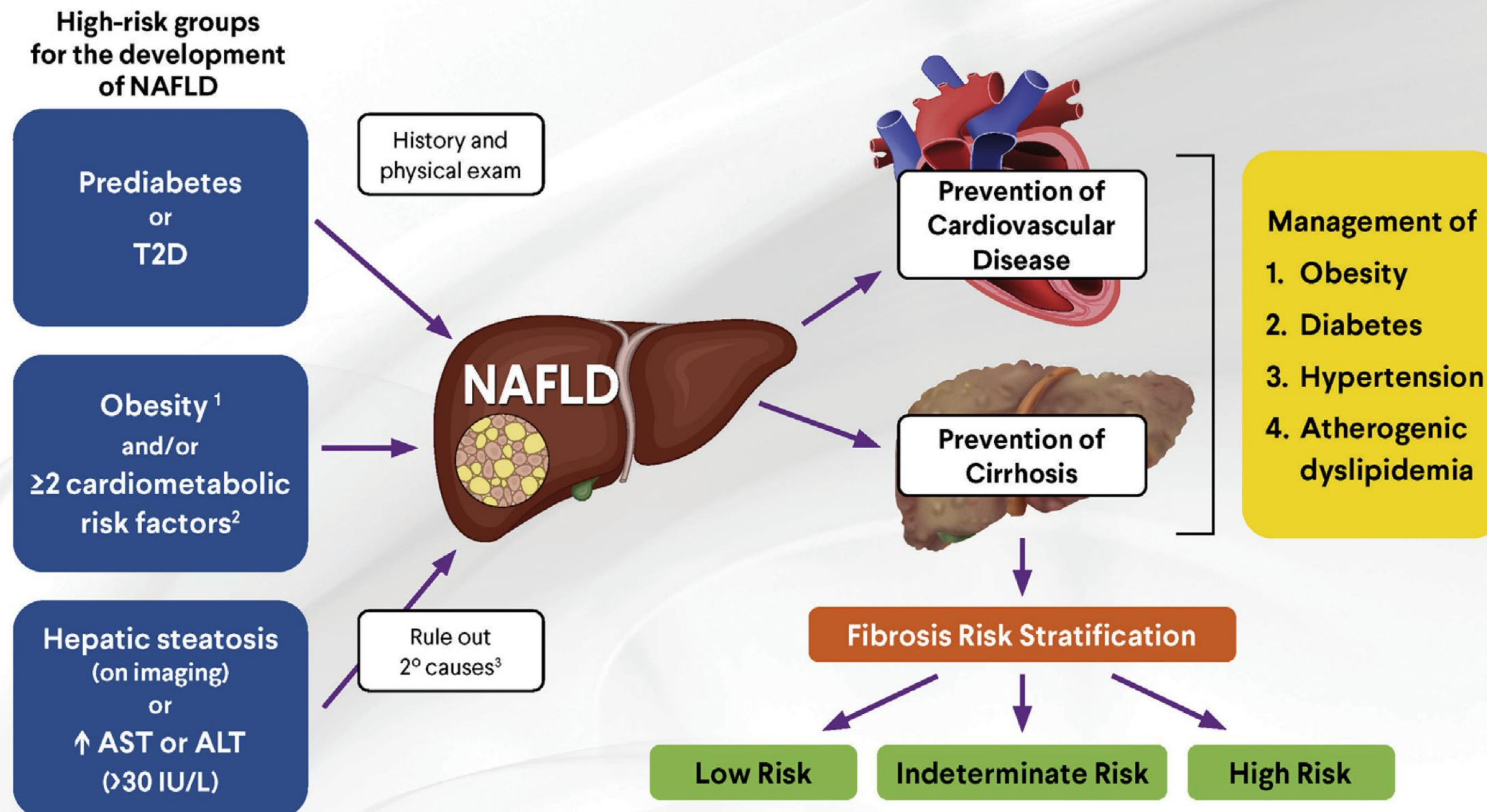
Micaela Gliozzi¹, Cristina Carresi¹, Vincenzo Musolino¹, Ernesto Palma¹, Carolina Muscoli¹, Cristiana Vitale², Santo Gratteri¹, Giuseppe Muscianisi¹, Elzbieta Janda¹, Saverio Muscoli³, Francesco Romeo³, Salvatore Ragusa¹, Rocco Mollace¹, Ross Walker¹, James Ehrlich¹, Vincenzo Mollace^{1*}

5. Conclusion

In conclusion, our data show that bergamot-deriving polyphenolic fraction given in patients with MS and NAFLD, leads to concomitant amelioration of the lipemic and glyceemic serum profile and to substantial reduction of liver steatosis. This effect, alongside with a reduction of pro-atherogenic small dense LDL and enhancement of anti-atherogenic high dense HDL, shed new light on the potential use of bergamot-extract for reducing cardiometabolic risk in patients with MS.

Non Alcoholic Fatty Liver Disease: esiste un ruolo per i nutraceutici?

Management Algorithm for NAFLD – Overview



Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T2D = Type 2 diabetes mellitus

- Adiposity-based chronic disease (ABCD) is a diagnostic term proposed by AACE to better describe the disease of obesity in a complication-centric manner of abnormal adipose tissue mass, distribution, function and resulting morbidity that can be ameliorated with weight loss.
- Cardiometabolic risk factors of the metabolic syndrome are waist circumference >40 inches men >35 inches women, triglycerides ≥150 mg/dL, HDL-C <40 mg/dL men, <50 mg/dL women, BP ≥130/≥85 mm Hg, fasting plasma glucose ≥100 mg/dL (NCEP ATP III)
- Secondary causes of liver steatosis or elevated transaminases (AST or ALT) are excessive alcohol consumption (≥14 drinks/week for women or ≥21 drinks/week for men), hepatitis B, hepatitis C (genotype 3), Wilson's disease, alpha 1 antitrypsin deficiency, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, hemochromatosis, mass lesions, medications and other causes.

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Algorithm Figure 1

Associazione tra dieta infiammatoria, HTN e steatosi epatica: un circolo vizioso?

ANNALS OF MEDICINE
2023, VOL. 55, NO. 1, 2195203

<https://doi.org/10.1080/07853890.2023.2195203>



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RESEARCH ARTICLE

 OPEN ACCESS



Association between dietary inflammation index and hypertension in participants with different degrees of liver steatosis

Wenhao Wu^a, Zhuoya Zhang^b, Yan Qi^a, Hua Zhang^a, Yuan Zhao^a and Jin Li^a

KEY MESSAGE

- Patients in the highest DII tertiles group had a higher SBP and higher rates of HTN compared with patients in the lowest DII tertiles group in male participants with severe hepatic steatosis S3.
- DII was positively associated with SBP and the prevalence of HTN in males with hepatic steatosis grade S3.
- The effect of DII on SBP and prevalence of HTN was significantly dependent on the severity of hepatic steatosis.

Messaggi chiave (1)

Il *Journal of the American College of Cardiology* in una recente review ha menzionato gli estratti di **bergamotto tra i nutraceutici raccomandati** per i pazienti intolleranti alle statine

Anche **acido ellagico** ed **esperidina** hanno evidenziato una loro attività sulla modulazione del profilo lipidico plasmatico in pazienti con livelli di colesterolo non elevato

I dati clinici osservati dopo assunzione dei singoli principi attivi, uniti al loro razionale biochimico e nutrizionale, suggeriscono che l'associazione di neoeriocitrina e naringina (da Bergamotto), acido ellagico (da Melograno) ed esperidina (da Arancio dolce) possa costituire un nutraceutico in grado di migliorare il profilo lipidico plasmatico (LDL-C, HDL-C, TG e ApoB) in **pazienti con dislipidemia lieve/moderata con o senza intolleranza alle statine**

Messaggi chiave (2)

Studi recenti hanno evidenziato una potenziale efficacia di neoeriocitrina e naringina (estratti dal bergamotto), acido ellagico ed esperidina sulle diverse componenti della **sindrome metabolica** (pressione arteriosa, TG e insulino-resistenza)

La **NAFLD** (steatosi epatica), patologia sempre più diffusa e senza un trattamento farmacologico specifico, è un'altra area di rilevante applicazione terapeutica dei nutraceutici, in particolare di quelli che hanno evidenziato un'**attività insulino sensibilizzante**

L'esecuzione di studi clinici ben disegnati per dimostrare l'efficacia dei **principi attivi in associazione**, di cui ad oggi non sono disponibili dati, rappresenterebbe un'attività di grande interesse scientifico e medico