

ALIMENTIAMO LA SALUTE, L'ALIMENTAZIONE NEI PERCORSI  
DI CURA ALL'INTERNO DELLA ASST DI MANTOVA  
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# Alimentazione nella patologia vascolare, nella sclerosi multipla e nel Parkinson

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# Outline



- Alimentazione nella prevenzione
  - primaria
    - l'esempio della malattia cerebrovascolare
  - secondaria/terziaria
    - l'esempio della sclerosi multipla
    - l'esempio della malattia di Parkinson



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# Alimento funzionale

Nel 1996 sotto il Coordinamento dell'ILSI Europe (International Life Style Institute) l'UE ha realizzato un *consensus document* della European Commission Concerted Action on Functional Food Science in Europe (FU.FO.S.E)



Un alimento può essere considerato funzionale se viene dimostrato in modo sufficiente che sia ***in grado di modificare in modo benefico una o più funzioni target dell'organismo, al di là del suo puro valore nutrizionale, in un modo che sia rilevante sia per il miglioramento dello stato di salute e/o di benessere e/o per la riduzione del rischio di malattia.*** Un alimento funzionale rimane un alimento e deve dimostrare il suo effetto in quantità che sono normalmente consumate nell'ambito di una dieta normale: non è una pillola, ma parte di un regime alimentare normale.

# Alimentazione & malattia cerebrovascolare

## Lipid-lowering effects

- Inhibition of cholesterol synthesis primarily through action on the enzyme HMG-CoA reductase (policosanols, polyphenols, garlic and red yeast rice)
- Increase in LDL receptor activity (berberine)
- Reduction of intestinal cholesterol absorption (garlic, plant sterols, fibers, probiotics)
- Ability to interfere with bile metabolism (probiotics, guggul).

## Blood pressure lowering

## Coadjuvant in diabetic complications

- Reducing hyperuricemia
- Improving insulin-resistance
- Reducing fasting blood-glucose



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# Alimentazione & malattia cerebrovascolare

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# Policosanoli

Estratto della matrice cerosa della canna da zucchero. Riduce la biosintesi del colesterolo mediante inibizione della sintesi dell'enzima HMG-CoA reductase. Si riduce la sintesi del mevalonato, da cui origina il colesterolo endogeno



- In the early 90s, a number of clinical studies suggested a lipid-lowering effect of policosanols in different types of patients (healthy volunteers, hypercholesterolemics, diabetics, or postmenopausal women), with reduction in LDL-cholesterol similar to that of statins (about 25%), and a 10% increase of HDL-C
- Nevertheless, studies were of limited samples, on a limited number of clinical centers, often in Cuba, and not confirmed by independent and external studies



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# Polyphenols

Very large family of substances available in the plant world



- Succo di limone → Naringina
- Melanzane → Nasnina
- Cipolle → Quercitina
- Vegetali → Luteolina
- Soia → Genisteina
- Uva → Resveratrolo
- The verde → Catechine
- Caffè → Acido clorogenico

# Polyphenols – succo di limone



## The Citrus Flavonoids Hesperidin and Naringin Do Not Affect Serum Cholesterol in Moderately Hypercholesterolemic Men and Women<sup>1-3</sup>

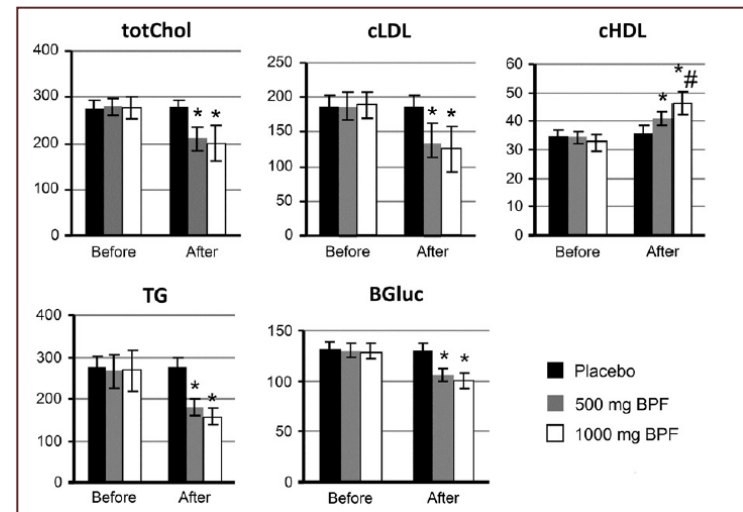
204 healthy men and women with a serum TC concentration of 5.0–8.0 mmol/L participated in a double-blind, placebo-controlled, randomized parallel design with 3 treatments: 4 capsules providing 800 mg/d of hesperidin, 4 capsules providing 500 mg/d of naringin, or 4 placebo capsules containing cellulose. Pure hesperidin and naringin consumed in capsules at mealtime do not lower serum TC and LDL-C conc in moderately hypercholesterolemic men and women.

	Control	Hesperidin	Naringin	<i>P</i> -value <sup>2</sup>
<i>n</i>	65	59	64	
TC, mmol/L	6.22 ± 0.05	6.19 ± 0.05	6.19 ± 0.05	0.864
LDL-C, mmol/L	4.00 ± 0.04	3.99 ± 0.04	3.99 ± 0.04	0.987
HDL-C, mmol/L	1.54 ± 0.02	1.53 ± 0.02	1.51 ± 0.02	0.375
TC/HDL-C	4.31 ± 0.05	4.29 ± 0.05	4.37 ± 0.05	0.516
TG, <sup>3</sup> mmol/L	1.26 ± 0.03	1.24 ± 0.04	1.28 ± 0.04	0.717

Demonty I et al *J. Nutr.* 140: 1615–1620, 2010

Hypolipemic and hypoglycaemic activity of bergamot polyphenols: From animal models to human studies

BPF, given orally for 30 days to 237 patients suffering from hyperlipemia either associated or not with hyperglycaemia reduces total and LDL cholesterol levels (an effect accompanied by elevation of cHDL, TG levels and by a significant decrease in blood glucose)



Mollace V et al. *Fitoterapia* 2011;82:309-316



# Red rice

The fermentation of red rice by a fungus (*Monascus purpureus*) produces a substance called monacolin K, which inhibits the synthesis of cholesterol. The monacolin K is also known as lovastatin, a statin available in the market worldwide.





# Berberina

This substance, with a bitter taste and intense yellow color, is present in the bark, roots and stems, including underground (rhizome) of plants of the genus *Berberis*, such as barberry (*Berberis vulgaris* L.).

Nutrition and Dietary Supplements

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REVIEW

## Berberine: metabolic and cardiovascular effects in preclinical and clinical trials

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Nutrition and Dietary Supplements  
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[Number of times this article has been viewed](#)

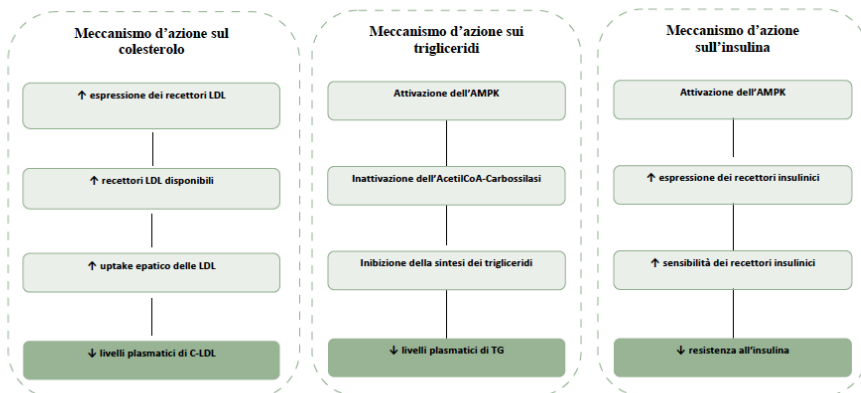
Arrigo FG Cicero<sup>1</sup>  
Sibel Ertek<sup>2</sup>

<sup>1</sup>Internal Medicine, Aging and Kidney Diseases Department, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy;  
<sup>2</sup>Ufuk University, Medical Faculty, Dr Ridvan Ege Hospital, Department of Endocrinology and Metabolic Diseases, Ankara, Turkey

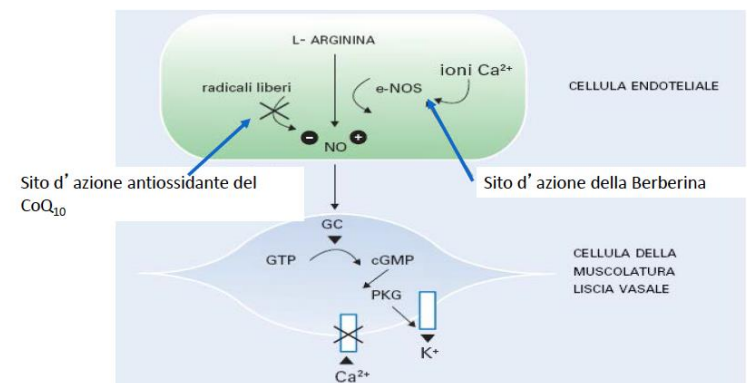
**Abstract:** Berberine is a plant alkaloid with numerous biological activities. A large body of preclinical *in vitro* and *in vivo* studies support different pharmacological actions of berberine that could be potentially useful in the management of metabolic diseases associated with high cardiovascular disease risk, such as mixed hyperlipidemia, insulin resistance, metabolic syndrome, and type 2 diabetes. Moreover, it seems that berberine also exerts anti-inflammatory and antiproliferative effects that could play a role in the development of atherosclerosis and its clinical consequences. Recently, the metabolic effects of berberine have been demonstrated in humans, opening new perspectives for the use of this molecule in patient therapy. Larger and longer clinical studies need to be carried out to implement the definition of the therapeutic role of berberine in humans.

**Keywords:** berberine, cardiovascular disease, diabetes, cholesterol

### Berberina: effetto sul colesterolo, trigliceridi e insulina



### Berberina e Coenzima Q10: effetto antipertensivo



# Sterols

Compete with cholesterol for absorption in the intestinal tract



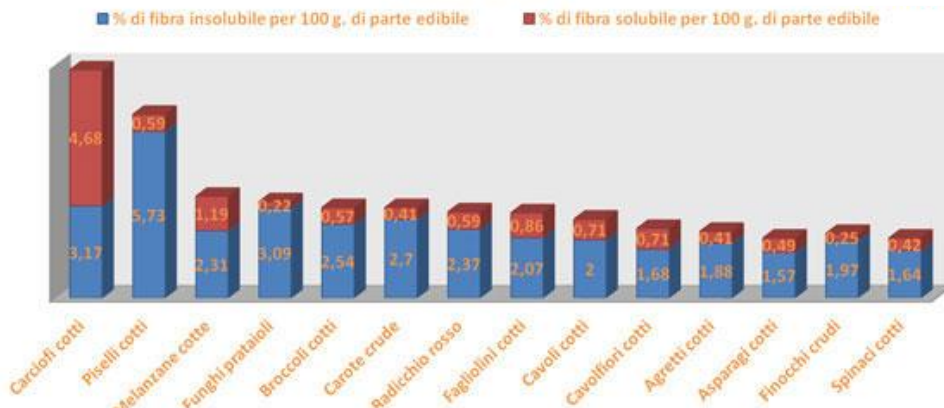
- Cereals: rice bran, wheat germ, oat bran, whole wheat, brown rice
- Legumes: dried peas, dried beans, lentils
- Nuts and seeds: peanuts, almonds, walnuts, pecans, sunflower seeds, pumpkin seeds, sesame seeds
- Fruits and vegetables (traces): broccoli, cauliflower, brussel sprouts, apples, avocados, tomato, vegetable oils, blueberries

The evidence for phytosterols is strong enough for the National Cholesterol Education Program to have added the recommendation to consume at least 2 grams per day if one's cholesterol is high. The Food and Drug Administration (FDA) also allows the following health claim on foods that meet the criteria: "Foods containing at least 0.65 gram per serving of vegetable oil plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 grams, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease."

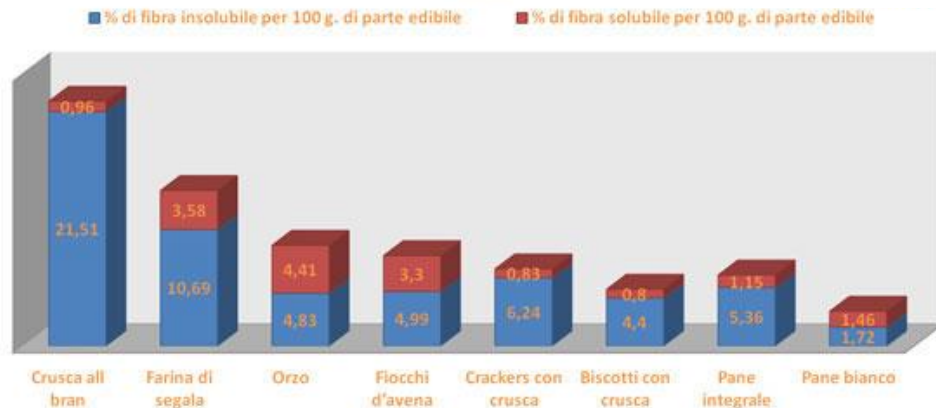
However, it would be difficult to consume much more than 500 milligrams (mg) of phytosterols daily from these food sources. Food manufacturers have also fortified a number of foods with phytosterols



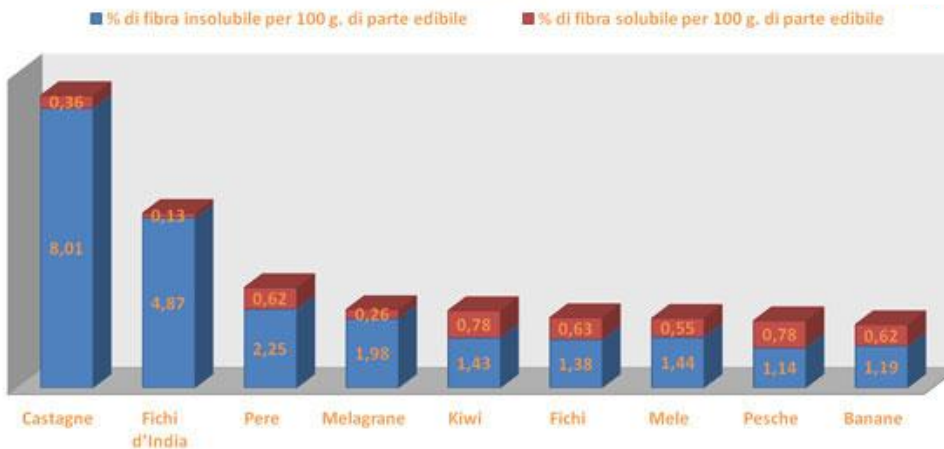
Verdure ed Ortaggi



Cereali



Frutta fresca



# Soluble fibers

Soluble fiber works a little differently from insoluble fiber: It takes up water in the digestive tract, forming a gummy, gel-like substance. While it, too, may help prevent constipation, a unique feature of soluble fiber is that it can help lower LDL cholesterol by binding to cholesterol in the intestines. The evidence for soluble fiber's cholesterol-lowering abilities is pretty strong and is supported by fairly extensive research.

How much soluble fiber does one need to lower LDL? Aiming for 7–13 grams of soluble fiber each day helps. Eating a total of 20–35 grams of fiber (both insoluble and soluble) each day can lower total cholesterol by 2% to 3% and LDL cholesterol by up to 7%. One way to get that much fiber in your meals is to eat at least 5 servings of fruits and vegetables a day, as well as 6 servings of grains.

# A Review of the Relative Efficacy of Dietary, Nutritional Supplements, Lifestyle and Drug Therapies in the Management of Hypertension

- Food derived bioactive peptide (Pripp 2008)

100-400 mL of fermented milk or hydrolyzed protein powder that contained 2.6 mg – 1500 mg of bioactive peptides x 4-12 weeks

- Garlic (Ried 2008)

Garlic powder, aged garlic extract, or distilled garlic oil. Dose: 12.3-2400 mg/day x 12-23 weeks

- Fibre (Streppel et al. 2005)

Insoluble and/or soluble fibre supplementation Average dose 11.5 g/day (3.5-42.6 g/day) x 2-24 weeks

- Semi di lino

- DASH Diet with and without sodium reduction (Sacks et al. 2001)

30 days/diet



Review

# Coadjuvants in the Diabetic Complications: Nutraceuticals and Drugs with Pleiotropic Effects



## RESVERATROL

1000 mg/day resveratrol in diet-controlled type-2 DM pts for 5 weeks did not change body weight, glycemic control or GLP-1 secretion. Thazhath SS et al. *Am. J. Clin. Nutr.* 2016;103:66–70

1500 mg/day of resveratrol for 4 weeks to obese pts had no effects on metabolic biomarkers, blood pressure or resting energy expenditure. Poulsen MM et al. *Diabetes* 2013, 62, 1186–1195.

Another study of patients with metabolic syndrome treated the pts with 1500 mg/day of resveratrol for 90 days revealed a significant reduction in body weight and insulin secretion



## FERMENTED MILK KEFIR

The kefir effects observed on primary outcomes included decreased fasting blood glucose and HbA1c levels as well as improved insulin resistance. Bourrie BC et al. *Front. Microbiol.* 2016, 7, 647.



## QUERCITINA

500 mg of daily quercetin (for 4 weeks) was capable of reducing hyperuricemia in healthy men, which is a relevant factor associated with insulin resistance and progression of diabetic complications. Shy Y et al. *Br. J. Nutr.* 2016;115:800–806.

Quercetin administered at the same dosage in women with type 2 DM, has been shown to decrease systolic arterial pressure, without significant effects on other cardiovascular risk factors. Zahedi M et al. *Int. J. Prev. Med.* 2013;4:777–785.

Another study reported no effect on flow-mediated dilation or insulin resistance with an analogue of quercetin (quercetin-3-glucoside, at 160 mg/day) in healthy men and women aged 40–80 years. Dower JI et al. *Am. J. Clin. Nutr.* 2015;101:914–921



# Quali evidenze nello prevenzione dello stroke?



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## CEREALI

2.5 vs 0.2 porzioni al giorno sono associati ad una riduzione del 37% di malattie cardiovascolari

*Mellen PB et al. Nutrition, Metabolism & Cardiovascular Diseases (2008) 18, 283.*



## FRUTTA e VEGETALI

L'assunzione di almeno 500 gr al giorno ha dimostrato un effetto protettivo nei confronti dell'ictus, in particolare per quanto riguarda i cruciferi, i vegetali a foglia verde e gli agrumi.

*Joshipura, JAMA 1999*



## CAFFE'

Una moderata assunzione è inversamente correlata all'incidenza di ictus e alla mortalità.

*Larsson SC, Orsini N. Am J Epidemiol 2011;174:993–1001*



## TE VERDE o NERO

L'assunzione di più di 4 tazze al giorno riduce del 20% il rischio di ictus .

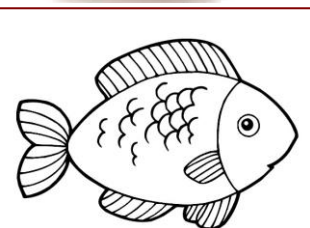
*Kokubo Y et al. Stroke. 2013;44:1369–1374. Larsson SC et al. Ann Epidemiol. 2013;23:157–160.*



## CIOCCOLATO

Il confronto tra diverse categorie di consumatori di cioccolato ha mostrato una riduzione del rischio del 19% nel gruppo di maggiori consumatori.

*Larsson SC. Stroke. 2014;45:309-314.*



## PESCE

Il pesce è ricco di acidi grassi polinsaturi che hanno attività antiinfiammatoria e riducono il volume della lesione ischemica in modelli sperimentali

*Lancette-Hebert M et al Stroke 2011;42:2903. Bazan NG et al. Experimental Neurology 2012;236:122*

# Come trasformare queste informazioni in consigli dietetici per prevenire lo stroke?



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# AHA-ASA guidelines 2014



It is reasonable to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet instead of a low-fat diet. The Mediterranean-type diet emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts. It limits intake of sweets and red meats (Class IIa; Level of Evidence C). (New recommendation)



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# Alimentazione & Multiple Sclerosis

- Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS), characterized by axonal injury and demyelination.
- MS is thought to result from a combination of genetic predisposition and environmental influences. Established environmental risk factors for MS include low vitamin D levels, sun exposure, smoking, and viral exposures (and obesity).
- In addition to the importance of environmental factors in risk of disease onset, there is significant variability among MS patients regarding clinical disease course.



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A growing body of literature suggests the importance of dietary factors in the risk of MS onset and clinical course

- ***Epidemiologic observations***

- ***Preclinical animal studies***

- ***Observational studies***

- HOLISM (Health Outcomes in a Sample of people with MS) study on 2047 patients with confirmed MS, who completed the Diet Habits Questionnaire (DHQ) as part of a comprehensive survey including information on relapse rate.
- NARCOMS (North American Research Committee on MS) on 6989 participants, who completed a dietary screener questionnaire (DSQ) in addition to providing information on recent relapses, progression, and disability.

- ***Small clinical trials***



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# Multiple Sclerosis Pathophysiology: Opportunities for Dietary Effects

## **1. modulate the inflammatory state**

MS was once considered strictly related to T cell dysregulation; however, many components of the innate and adaptive immune systems have now been shown to be relevant to MS immunopathology.

Dietary factors that are able to promote regulatory as opposed to inflammatory immune cell differentiation and cytokine production therefore have the potential ability to reduce new inflammatory lesion formation and clinical relapses

## **2. protect against neurodegeneration**

Approximately 10% of patients present with progressive neurological decline from the outset. Even in patients with a relapsing-remitting phenotype, the neurodegenerative aspect of the disease is present early on and is in fact detectable before the disease becomes clinically apparent. According to a model with increasing support, oxidative stress causes mitochondrial dysfunction resulting in chronic energy insufficiency, eventually leading to ion channel redistribution causing cell damage and eventually cell death

## **3. promote nervous system repair**

Remyelination of demyelinated axons may be helpful with regard to restoring function as well as with protection of previously denuded axons from further damage. The process of remyelination occurs spontaneously however is highly variable between individuals and efficiency decreases over time. Oligodendrocyte precursor cells (OPCs) capable of remyelination are present in the adult brain; however, inhibitors of OPC differentiation in the local environment hinder this process

# Evidence for the Role of Specific Dietary Components in MS

- **Saturated Fat**

- It is generally accepted that intake of saturated fats increases LDL cholesterol, which is associated with poor outcomes in MS
- Fatty acid chain length seems to be an important determinant of ultimate effects
  - Mice fed an LCFA-rich diet exhibited more severe EAE compared to those fed a standard diet. In contrast, short- chain fatty acids (SCFAs) have been demonstrated to favor differentiation of regulatory T cells with resulting production of anti-inflammatory cytokines. Rather than being ingested in the diet, SCFAs are largely produced by intestinal microbiota in response to dietary intake of fiber-rich plant-based foods.
- Swank diet with reduced saturated fat (< 20 g/day) intake. Those who adhered to the diet showed significantly less disability and had lower mortality rates those who did not. However, lack of randomization or measurement of potential confounding factors makes these results difficult to interpret

- **Dairy**

- Conflicting results

- **Fruits, vegetables, and whole grains**

- In the HOLISM study higher intake of fruits and vegetables was associated with reduced levels of patient reported disease activity and disability
- The prospective pediatric MS study noted a reduction in relapse rates with increasing intake of vegetables.
- NARCOMS study noted an inverse relationship between whole grain intake and MS-related disability.

- **Salt**

- Preclinical studies have suggested potential adverse effects of a high salt diet in MS.
- Conflicting results from observational studies.

# Dietary Patterns in Multiple Sclerosis

## ***HOLISM (Health Outcomes in a Sample of people with MS) study***

Every 10-point increase on the DHQ (overall score ranging from 0 to 50, higher scores indicating higher quality diet) was associated with a 30% less likelihood of higher disability level. Higher DHQ scores were also significantly associated with better physical and mental health-related quality of life (HRQOL).

## ***NARCOMS (North American Research Committee on MS)***

Participants in the top quintile of diet quality score were at 20% lower odds of higher disability scores compared to those in the bottom quintile. Higher diet quality was also linked to decreased odds of more severe depressive symptoms, after adjusting for disability status.



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- ***Caloric restrictions***

A current pilot study is evaluating feasibility and effects of continuous and intermittent caloric restriction compared to controls for approximately 1 year in MS patients (NCT02647502).

- ***McDougall diet***

The McDougall Diet is a very low-fat (10% of calories from fat) diet consisting mostly of starchy plant-based foods as well as other vegetables and fruits. No animal products or oils are permitted. In a recent study, 61 participants with RR MS were randomized to follow the McDougall diet or participate as a wait-list control for 12 months. The primary end point, the number of new T2 lesions on MRI, was not satisfied; however, notably the study was powered to detect only a very large effect. There were no differences in clinical relapse rates. There was a significant impact on fatigue, though much of the effect was attributable to weight loss. A larger randomized trial of this diet for fatigue is currently underway (NCT03322982).

- ***Paleolithic diets***

They generally emphasize consumption of lean meats including organ meats, fish, vegetables, and fruits and typically do not permit consumption of dairy or grain products. Studies are currently underway (NCT02687919, NCT02914964).

- ***Mediterranean diet***

There has been little work on Mediterranean-style diets in MS. However, the preliminary evidence regarding the role of various dietary components suggests that this type of diet may be of benefit. Mediterranean-style diets are low in saturated fats, high in polyunsaturated and monounsaturated fats (especially fish and olive oil), high in fruits and vegetables, and low in processed foods implying low salt content. A pilot clinical trial of a modified Mediterranean diet in MS is currently underway (NCT02986893).

# Alimentazione & Malattia di Parkinson

Nella malattia di Parkinson il raggiungimento e il mantenimento di un adeguato stato nutrizionale influenza direttamente e positivamente l'evoluzione clinica della patologia. Inoltre una corretta alimentazione influenza l'efficacia della terapia farmacologica.

Il 65% dei pazienti affetti da malattia di Parkinson presenta alterazioni dello stato nutrizionale.

- Nelle fasi più precoci della malattia è frequente il riscontro di sovrappeso o di obesità e delle alterazioni metaboliche e vascolari associate
- Con il progredire della patologia e della sua gravità, la perdita di peso e il rischio di malnutrizione aumentano in modo lineare.

Fattori che determinano un aumentato dispendio energetico

- Discinesie
- Tremori
- Rigidità, ipertono
- Fisiochinesiterapia

Fattori che determinano un ridotto apporto di nutrienti

- Depressione
- Fattori fisici (scialorrea, disfagia, nausea, stitichezza, ...)
- La levodopa

# Alimentazione & Malattia di Parkinson – Finalità specifiche

- Raggiungimento e stabilizzazione del peso corporeo auspicabile
- Prevenzione di malattie metaboliche (dislipidemie, diabete, gotta), cardiovascolari ed osteoarticolari
- Supporto nel controllo di sintomi quali la disfagia, la stipsi e il rallentato svuotamento gastrico
- Ottimizzazione dell'efficacia della terapia con levodopa



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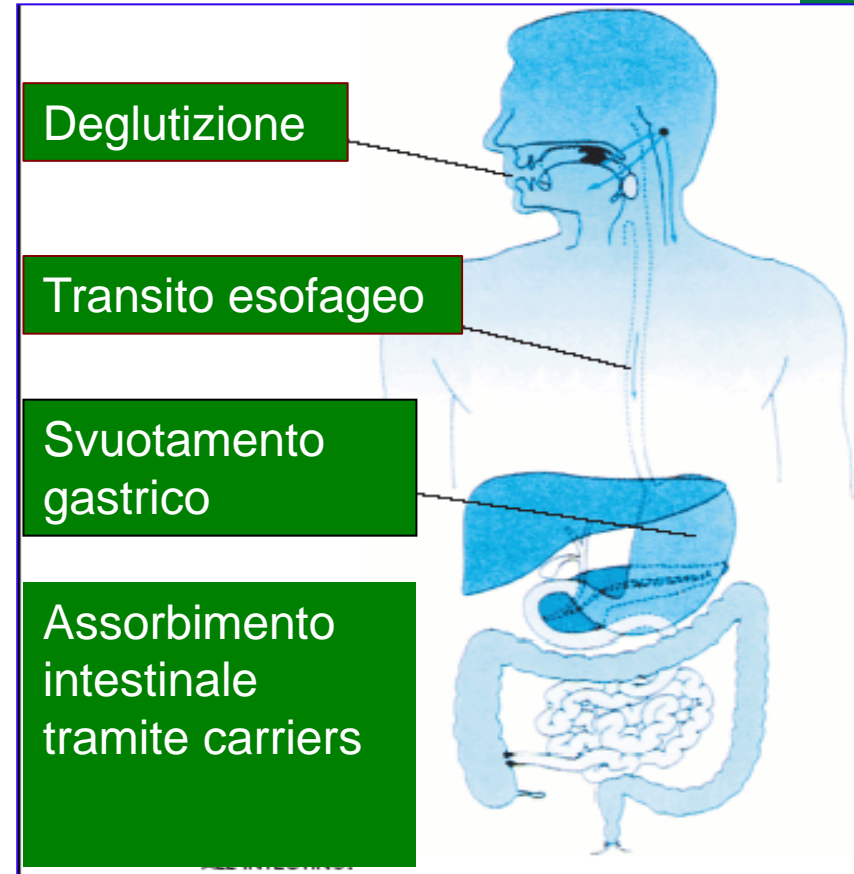
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# Alimentazione & levodopa

- La *levodopa* è un aminoacido neutro che necessita di un sistema di trasporto attivo (*carrier*) per il passaggio dall'intestino al sangue e da questo al comparto encefalico
- Tutti gli aminoacidi simili, provenienti dalle proteine ingerite con il pasto, si pongono in competizione per i *carriers* specifici rendendoli meno disponibili al trasporto della levodopa
- Un rallentato svuotamento gastrico determina una maggior esposizione della levodopa alla dopadecarbossilasi (che converte la levodopa in dopamina rendendola non disponibile all'assorbimento intestinale)



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# Fattori alimentari che hanno effetto sulla risposta alla somministrazione di L-Dopa



Calcolare il fabbisogno proteico e ottimizzare la ripartizione delle proteine alimentari nei vari pasti della giornata in relazione alla terapia con levodopa

Considerare gli effetti del cibo sullo svuotamento gastrico

- energia degli alimenti
- volume e composizione pasti
- viscosità degli alimenti

- Una restrizione delle proteine alimentari nella prima parte della giornata (fino alla 17) si è rivelata utile per migliorare l'efficacia della terapia nei casi in cui sono presenti importanti fluttuazioni motorie.
- La quantità totale di proteine non deve essere inferiore a 0.8 g/kg di peso corporeo ideale per evitare stati carenziali e malnutrizione (gli alimenti proteici sono anche fonte di ferro e calcio)
- Inibiscono lo svuotamento gastrico i grassi alimentari, le fibre, l'eccessiva acidità gastrica e i farmaci ad azione anticolinergica

# Take home messages

Una malattia può avere mille padri, ma una sola madre: l'alimentazione squilibrata

Il segreto per vivere a lungo è: mangiare la metà, camminare il doppio, ridere il triplo e amare senza misura.



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