



**XXII Congresso Nazionale Società Italiana di Pediatria
Preventiva e Sociale**

**OLIO EXTRAVERGINE D'OLIVA: ASPETTI NUTRACEUTICI
Caramia G.**

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LO SQUALENE

- **Triterpene:** composto intermedio nella biosintesi degli steroli largamente distribuito in natura
- **Abbondante nel fegato di squalo:** → nome
- **Componente più abbondante dei composti minori:** 1 e 20 g/kg di olio in funzione della varietà
- **Presenza di isomeri e idrossi derivati:** "marker" di processo di rettificazione
- **Ghiandole sebacee: rappresenta il 12% del secreto:**
 - * funzione antiossidante protettiva del derma
 - * trattiene la naturale umidità della pelle contro le radiazioni solari, = filtro biologico.
 - * protegge lo strato corneo della pelle da prodotti chimici, detergenti, traumi ecc.

(Viola, 2009)



Ryszard Amarowicz



Chemical structure of squalene

Editorial

Squalene: A natural antioxidant?

Squalene (see left) is a triterpene and an intermediate in the plant and animal world [1]. The richest known source of squalene is shark liver oil. Squalene is found over broad ranges [2]. For example, in flaxseed oil it is not detected, but is quite prominent in peanut (1.28 g/kg) and olive (5.99 g/kg) oils. Squalene is the main component of skin lipids. Squalene shows some advantages for the skin as an emollient and a natural terpene has also been found to have protective activity against oxidative damage [3].

Conforti *et al.* [4] reported an antioxidant effect of squalene in liposomes; the IC₅₀ value for squalene was 0.023 mg/mL. The antioxidant activity of *anthus caudatus* examined using the same method was 20-fold higher than that of α -tocopherol by squalene in photo-oxidation studies was studied by Sudo [5]. This is in line with the hypothesis of Kohno *et al.* [6].

Squalene showed slight antioxidant activity when assayed against peroxidation of linoleic acid [7]. In the same study, squalene demonstrated a synergistic effect with β -sitosterol. The authors suggested that squalene could act as a natural antioxidant by scavenging free radicals and by inhibiting the oxidation of lipids.

In summary, squalene is a hydrophilic natural antioxidant

LO SQUALENE

- **Sebo umano-olio oliva:** contenuto simile di squalene
→ ingrediente naturale di prodotti biocosmetici
 - **Cleopatra prima crema anti rughe:** olio d'oliva, latte, incenso e bacche di ginepro.
- **Secrezione sebo e concentrazione squalene:** diminuisce nella cute dell'anziano → manca effetto antiossidante, ritenzione idrica, manca la formazione del filo idrolipidico, indebolito da raggi solari e detergenti.
- **Contribuisce:** a già nota attività anti-cancerogena
(Owen, 2000; Waterman, 2007)

---- La cosa più difficile è vedere quello che abbiamo sempre sotto gli occhi. Goethe

LO SQUALENE

- Effetto protettivo sulla

fotocarcinogenesi: fenoli + squalene bloccano il danno ossidativo sul DNA foto-indotto

(Owen, 2000; Waterman, 2007, Sotiroudis 2008)

- **Concorre a ridurre:** PA, peso, colesterolo, trigliceridi, glicemia e livelli plasmatici di leptina

(Liu Y, 2009)

---- L'ignoranza e l'intelligenza hanno una sola cosa in comune: sono senza limite.

OBESITA' INFIAMMAZIONE E APPETITO RUOLO NUTRACEUTICO DELL'OLIO EXTRAVERGINE D'OLIVA (VOO)

- **Tessuto grasso bianco:** non solo accumulo di lipidi ma organo endocrino con ruoli nei meccanismi infiammatori e metabolici

(Bulló, 2007;

Wozniak, 2008)

- **Adipociti producono più di 50 adipochine che liberano:** proteine chemotattiche, del complemento (adipsina), di controllo PA, angionenesi, metabolismo glucosio e lipidi (adiponectina, resistina, visfatina, apelina, vaspina, hepcidina, chemerina, omentina)

(Wozniak, 2008; Fukuhara, 2005)

OBESITA' E INFIAMMAZIONE

- Liberano proteine:

- pro coagulanti: PAI-1, fattore VII, enzima ossido nitrico sintetasi → maggior rischio malattie cardiovascolari negli obesi;

- citochine con attività pro-infiammatoria: leptina, proteina-1 chemoattrattiva dei monociti, TNF-alfa e IL-6, → flogosi cronica

- Favoriscono:

resistenza all'insulina, il diabete tipo 2 e sindrome metabolica

(Cinti, 2005; Bulló, 20007; Wozniak, 2008)

OBESITA' E INFIAMMAZIONE

- **Livelli sierici adipochine pro infiammatorie (visfatina):**

*primo passo cascata infiammatoria,

*correlati con quantità grasso viscerale e sono elevati nell'obeso, nel diabete tipo 2, nei soggetti a rischio di malattie coronariche, artrite reumatoide ecc.

(Bulló, 2007; Fukuhara, 2005).

- **Composti minori VOO:** fenoli, carotenoidi, tocoferoli ecc, inibiscono l'attivazione del NF-kB → proteggono mitocondri, riducono radicali liberi, ossidazione DNA, fabbisogno insulina, migliorano profilo lipidico e indice glicemico, potenziano azione insulina, migliorano metabolismo lipidico

(Cicerale, 2009; Brunelleschi, 2007).

BRIEF COMMUNICATIONS

Ibuprofen-like activity in extra-virgin olive oil

Enzymes in an inflammation pathway are inhibited by oleocanthal, a component of olive oil.

Newly pressed extra-virgin olive oil contains oleocanthal — a compound whose pungency induces a strong stinging sensation in the throat, not unlike that caused by solutions of the non-steroidal anti-inflammatory drug ibuprofen¹. We show here that this similar perception seems to be an indicator of a shared pharmacological activity, with oleocanthal acting as a natural anti-inflammatory compound that has a potency and profile strikingly similar to that of ibuprofen. Although structurally dissimilar, both these molecules inhibit the same cyclooxygenase enzymes in the prostaglandin-biosynthesis pathway.

The agent in extra-virgin olive oil responsible for throat irritation is thought to be the dialdehydic form of (–)deacetoxy-ligstroside aglycone² (or oleocanthal, with oleo- for olive, -canth- for sting, and -al for aldehyde) (Fig. 1). To confirm this, we isolated (–)oleocanthal from different premium olive oils and measured its intensity as a throat irritant. We found that irritation intensity was positively correlated with oleocanthal concentration. Although this finding indicates that oleocanthal is probably the principal irritating compound in olive oil, it was possible that

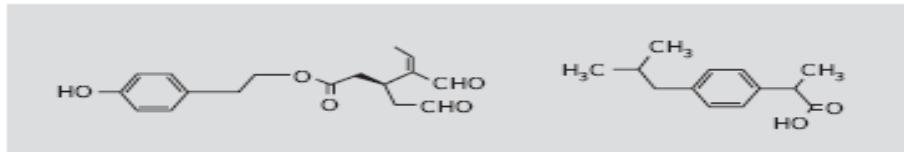


Figure 1 | Structures of (–)oleocanthal (left) and the anti-inflammatory drug ibuprofen (right). How they underpin the similar throat-irritating and pharmacological properties of the two compounds is unclear as yet.

co-elution of a minor component or a mixture of components could be causing the burning sensation². We therefore completed a *de novo* synthesis of oleocanthal, assigned the absolute stereochemistry (A.B.S. and Q.H., unpublished results), and tested the throat-irritant properties of this synthetic (–)oleocanthal, dissolved in non-irritating corn oil. The effect was comparable to that of premium extra-virgin olive-oil oleocanthal and was dose-dependent. (For details and for methods, see supplementary information.)

Forty years ago, it was found that the bitterness of certain compounds correlated with their pharmacological activity³. On the basis of their shared irritant properties, we therefore tested whether oleocanthal might mimic the pharmacological effects of ibuprofen (Fig. 1), a potent modulator of inflammation and analgesia⁴. Ibuprofen is a non-selective

inhibitor of the cyclooxygenase enzymes COX-1 and COX-2, but not of lipoxygenase⁴, which catalyse steps in the biochemical inflammation pathways derived from arachidonic acid. We found that, like ibuprofen, both enantiomers of oleocanthal caused dose-dependent inhibition of COX-1 and COX-2 activities but

had no effect on lipoxygenase *in vitro* (Table 1).

Our findings raise the possibility that long-term consumption of oleocanthal may help to protect against some diseases by virtue of its ibuprofen-like COX-inhibiting activity^{5,6}. If 50 g of extra-virgin olive oil containing up to 200 µg per ml oleocanthal is ingested per day⁷, of which 60–90% is absorbed^{8,9}, then this corresponds to an intake of up to 9 mg per day. This dose is relatively low, corresponding to about 10% of the ibuprofen dosage recommended for adult pain relief, but it is known that regular low doses of aspirin, for example, another COX inhibitor, confer cardiovascular health benefits¹⁰. Ibuprofen is associated with a reduction in the risk of developing some cancers⁵ and of platelet aggregation in the blood¹¹, as well as with the COX-independent secretion of amyloid-β42 peptide in a mouse model of Alzheimer's disease⁶. A Mediterranean diet, which is rich in olive oil, is believed to confer various health benefits, some of which¹² seem to overlap with those attributed to non-steroidal anti-inflammatory drugs.

Our discovery of COX-inhibitory activity in a component of olive oil offers a possible mechanistic explanation for this link.

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Table 1 | Selective inhibition of COX enzymes by oleocanthal enantiomers

Agent	Concentration (µM)	COX-1 (%)	COX-2 (%)	15-LO (%)
(–)Oleocanthal	100	83.5 ± 3.5	70.9 ± 8.6	0.4 ± 0.8
	25	56.1 ± 3.2	56.6 ± 9.5	0.0 ± 0.0
	7	24.6 ± 7.3	14.5 ± 2.3	0.0 ± 0.0
(+)Oleocanthal	100	68.0 ± 15.2	69.6 ± 3.9	3.5 ± 5.5
	25	54.5 ± 4.6	41.3 ± 15.9	0.7 ± 1.0
	7	24.6 ± 7.5	6.1 ± 4.2	0.0 ± 0.0

BRIEF COMMUNICATIONS

Ibuprofen-like activity in extra-virgin olive oil

Enzymes in an inflammation pathway are inhibited by oleocanthal, a component of olive oil.

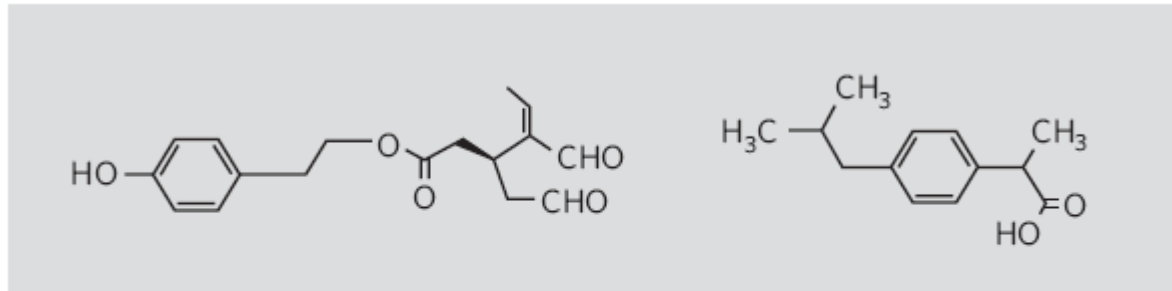


Figure 1 | Structures of (–)oleocanthal (left) and the anti-inflammatory drug ibuprofen (right). How they underpin the similar throat-irritating and pharmacological properties of the two compounds is unclear as yet.

Decarbossimetil-ligstroside aglicone detto anche **Oleocantale**

--- Non c'è sogno che non possa essere sognato
purché si sappia sopportarne l'alba. C. Calandra

Our findings raise the possibility that long-term consumption of oleocanthal may help to protect against some diseases by virtue of its ibuprofen-like COX-inhibiting activity^{5,6}. If 50 g of extra-virgin olive oil containing up to 200 µg per ml oleocanthal is ingested per day⁷, of which 60–90% is absorbed^{8,9}, then this corresponds to an intake of up to 9 mg per day. This dose is relatively low, corresponding to about 10% of the ibuprofen dosage recommended for adult pain relief, but it is known that regular low doses of aspirin, for example, another COX inhibitor, confer cardiovascular health benefits¹⁰. Ibuprofen is associated with a reduction in the risk of developing some cancers⁵ and of platelet aggregation in the blood¹¹, as well as with the COX-independent secretion of amyloid-β42 peptide in a mouse model of Alzheimer's disease⁶. A Mediterranean diet,

Healthy effects of olive oil	Hypothesized mechanism
Blood pressure	Polyphenols of olive oil affect blood pressure by a mechanism involving the cAMP dependent protein Kinase A and the Rho Kinase, two major regulators of the vascular smooth muscle contraction
Glucose metabolism	There is a protective effect of olive oil on the development of type II diabetes. The existence of an interaction between pro12Ala polymorphism of PPAR γ 2 and dietary MUFA has been suggested
Lipoprotein profile	Virgin olive oil with high phenolic content is effective in protecting LDL from oxidation and rising HDL cholesterol levels
Thrombotic profile	Antithrombotic properties of olive oil are mediated by the reduction in fibrinogen concentration and the impairment in the platelet/vessels wall interaction
Cancer development	The mechanism by which the cancer preventing effects of olive oil can be performed are still unknown. The hypothesis is related to the regulation of cancer related oncogenes.
Immune function	Increased olive oil consumption is implicated in the modulation of the immune function, particularly the inflammatory processes associated with the immune system. There are many studies that prove that phenolic compounds can decrease the production of lymphocyte-derived cytokines such as INF-gamma
Oxidative stress	The antioxidant effects of olive oil are due to the combination of its high oleic content (low oxidation potential compared with linoleic acid) and its content of a variety of antioxidants, in particular hydroxytyrosol and tyrosol.



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Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor

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Abstract

Oleuropein, a non-toxic secoiridoid derived from the olive tree, is a powerful antioxidant and anti-angiogenic agent. Here, we show it to be a potent anti-cancer compound, directly disrupting actin filaments in cells and in a cell-free assay. Oleuropein **inhibited the proliferation and migration of advanced-grade human tumor cell lines in a dose-responsive manner.** In a novel tube-disruption assay, Oleuropein irreversibly rounded cancer cells, preventing their replication, motility, and invasiveness; these effects were reversible in normal cells. **When administered orally to mice that developed spontaneous tumors, Oleuropein completely regressed tumors in 9–12 days.** When tumors were resected prior to complete regression, they lacked cohesiveness and had a crumbly consistency. No viable cells could be recovered from these tumors. **These observations elevate Oleuropein from a non-toxic antioxidant into a potent anti-tumor agent with direct effects against tumor cells.** Our data may also explain the cancer-protective effects of the olive-rich Mediterranean diet.

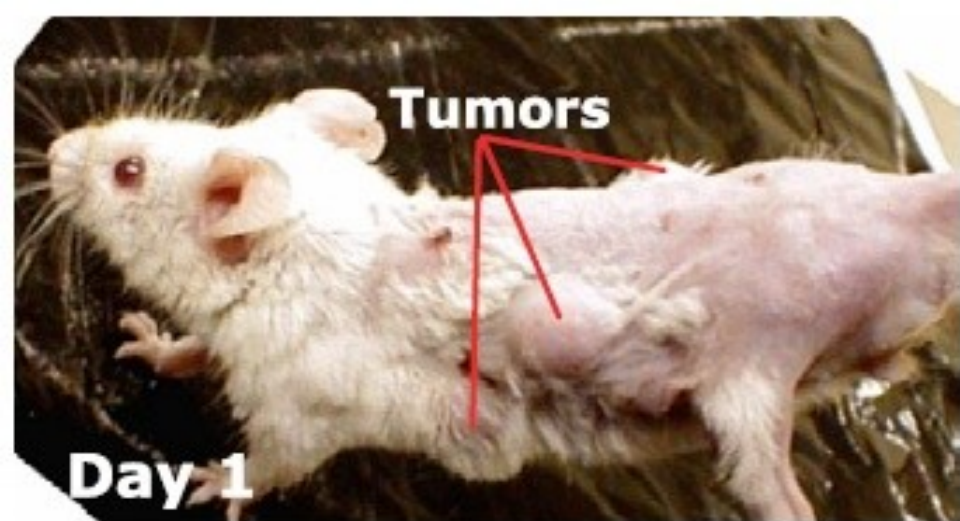


Fig. 8. Oleuropein induces tumor regression in vivo. Mice bearing spontaneous tumors were administered 1% Oleuropein in their drinking water. Some mice had multiple tumors (represented by mouse A), whereas others bore a single tumor mass (represented by mouse B). After 9–12 days of treatment, tumors had completely regressed.

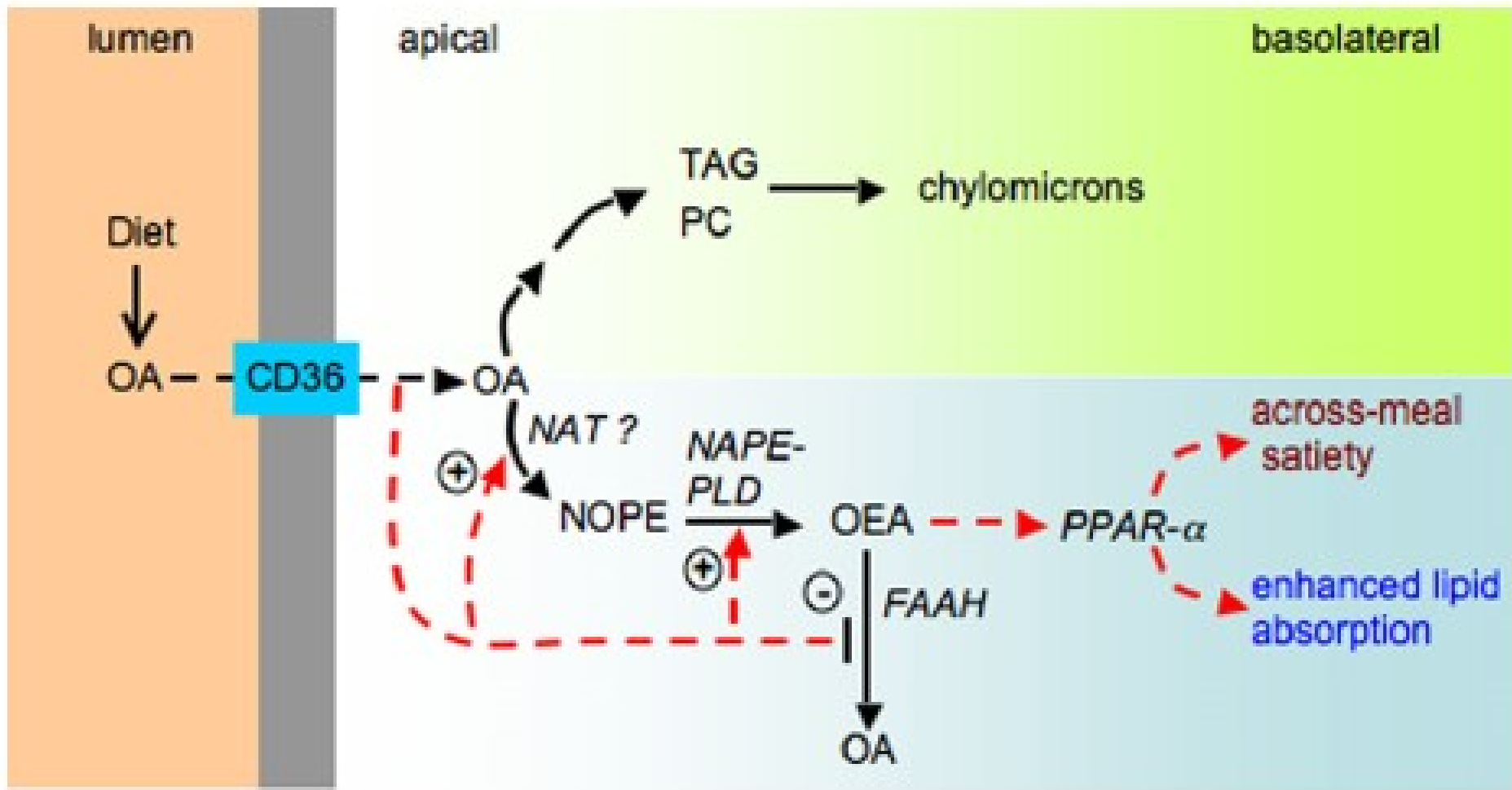
SENSO DI SAZIETA'

- **Ac.oleico** → **oleoiletanolamide (OEA)**: determina senso di sazietà, prolunga intervallo tra un pasto e l'altro.
- **Entrato negli enterociti duodeno-digiuno**, → OEA, azione ormonosimile anoressizzante senza interferire su assunzione di liquidi, attività motoria, stato d'ansia, livelli ormonali da stress

(Fu,2005; LoVerme,2005; Piomelli,2008; Schwartz,2008)

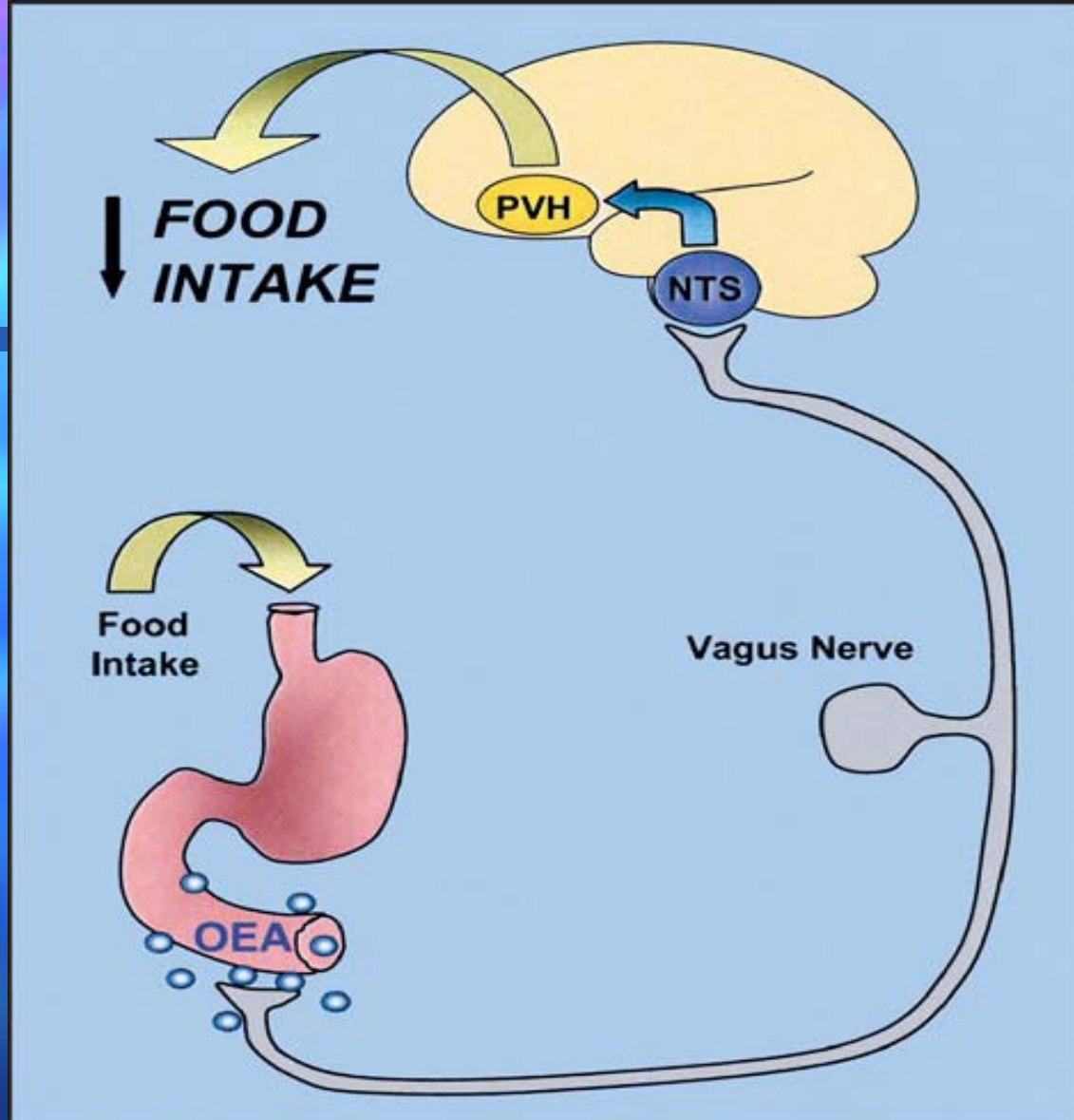
- **Azione OEA**: attivazione recettori intestinali PPAR-alfa, coinvolgimento fibre vagali che portano lo stimolo al Nucleo del Tratto Solitario (NST) alla base del cervello e, quindi al nucleo Paraventricolare Ipotalamo (PVH)
→ senso di sazietà con blocco assunzione cibo

(Schwartz, 2008)



----A thing of beauty is a joy for ever.

R. Kipling



---- L'esperienza è un pettine che la vita ti dà quando hai perso i capelli
André Mourois

COLESTEROLO E FITOSSTEROLI

- **Aterosclerosi da ipercolesterolemia:** prima causa di morte nei paesi industrializzati.
- **Italia 150.000 persone sono colpite da infarto (IMA):** e 4.4 per mille soggetti affetti da invalidità cardiovascolare
- **USA:** 7.1 milioni affetti da cardiopatia ischemica, 4.9 da insufficienza cardiaca postinfartuale con mortalità 50% dopo 5 anni
- **Contenuto:** 7% nel sangue, 93% nelle membrane cellulari dove è costituente principale, in particolare nel tessuto nervoso (17% del residuo secco del cervello)
- **Coinvolto nella sintesi ormoni steroidei e sali biliari**

COLESTEROLO E FITOSSTEROLI

- **Colesterolo non tutto nocivo:** l'HDL

l'eliminano per vie biliari

- **Aumento colesterolo:** da alterazione

tra assunzione, biosintesi endogena ed eliminazione con
bile e feci → lesioni vascolari,

ischemie, trombosi o infarti

- **Fitosteroli:** composti vegetali lipofili ampiamente
distribuiti nel regno vegetale con struttura analoga al
colesterolo ma con proprietà ipocolesterolemizzanti
→ produzione di fitosteroli da oli vegetali e loro
inserimento pane, pasta, yogurt, latte, salse, condimenti,
ecc.

(Ellegard, 2007; Lichtenstein, 2006)

COLESTEROLO E FITOSSTEROLI

- **Colesterolo e fitosteroli:** struttura simile ma assorbiti e metabolizzati dall' uomo con efficienza diversa.
- **Assorbimento:** colesterolo varia da il 20 e l'80%, fitosteroli da 2-5% anche con dosi superiori a 3g/die (Ellegård, 2007; Lichtenstein, 2006).
- **Maggior contenuto di fitosteroli:** oli vegetali, frutta a guscio, verdure (Tab. 1) per cui, nei Paesi occidentali, l'apporto complessivo con la dieta è simile a quello del colesterolo (150-400 mg/die), aumentato di circa un 50% nel caso delle diete vegetariane .

Grassi e olii		Frutta		Verdure	
Olio di arachide	258	Arance	24	Broccoli	39
Olio di colza	668	Fichi	22	Carote	16
Olio di girasole Bruxelles 43		411	Limoni	18	Cavolini
Olio di mais	909	Mandorle	183	Cavolfiore	40
Olio di oliva	154	Mele	13	Funghi	18
Olio di palma	39	Noci	127	Olive, verdi	35
Olio di soia	320	Pesche	15	Olive, nere	50

COLESTEROLO E FITOSSTEROLI

- **Apporto di fitosteroli con VOO:** discreta quantità, miglior assorbimento in quanto dispersi nei lipidi, assenza di reazioni allergiche da proteine possibili con i fitosteroli derivati da soia ed arachidi e perché non riducono i livelli di vitamina E (α -tocoferolo)

(Lichtenstein, 2006)

- **Fitosteroli VOO:**

riducono colesterolemia per sinergia con abbondante contenuto di acido oleico, potenziano l'azione anti infiammatoria e anti ossidante dei composti minori (derivati dell'oleuropeina, oleocantale ecc.).

----- **Quelli che s'innamoran di pratica senza scienza son come'l nocchiero ch'entra in naviglio senza timone o bussola, che mai ha certezza dove si vada.**

----Nulla possono gli Dei contro l'ignoranza degli uomini

---- La ignoranza e l'intelligenza hanno una sola cosa in comune: sono senza limite. Anonimo

... Non c'è nulla di più pericoloso di una ignoranza attiva. Goethe

---- L'ignoranza e l'intelligenza hanno una sola cosa in comune: sono senza limite.

Anonimo

