III SIMPÓSIO INTERNACIONAL
EM INVESTIGAÇÕES
QUÍMICO-FARMACÊUTICAS

I ENCONTRO IBERO-AMERICANO
DE PLANTAS MEDICINAIS DR. MAHABIR GUPTA

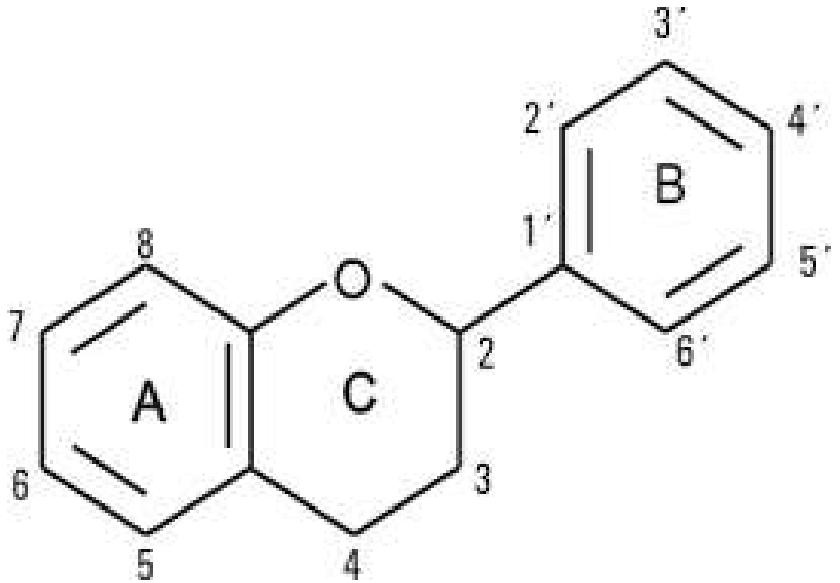
I CONGRESSO LUSO-BRASILEIRO
DE CIÊNCIAS E TECNOLOGIAS EM SAÚDE

28 a 30 de setembro de 2022, Itajaí-SC-Brasil

ACTIVIDAD ANTIINFLAMATORIA DE FLAVONOIDES. ROL POTENCIAL CONTRA COVID-19

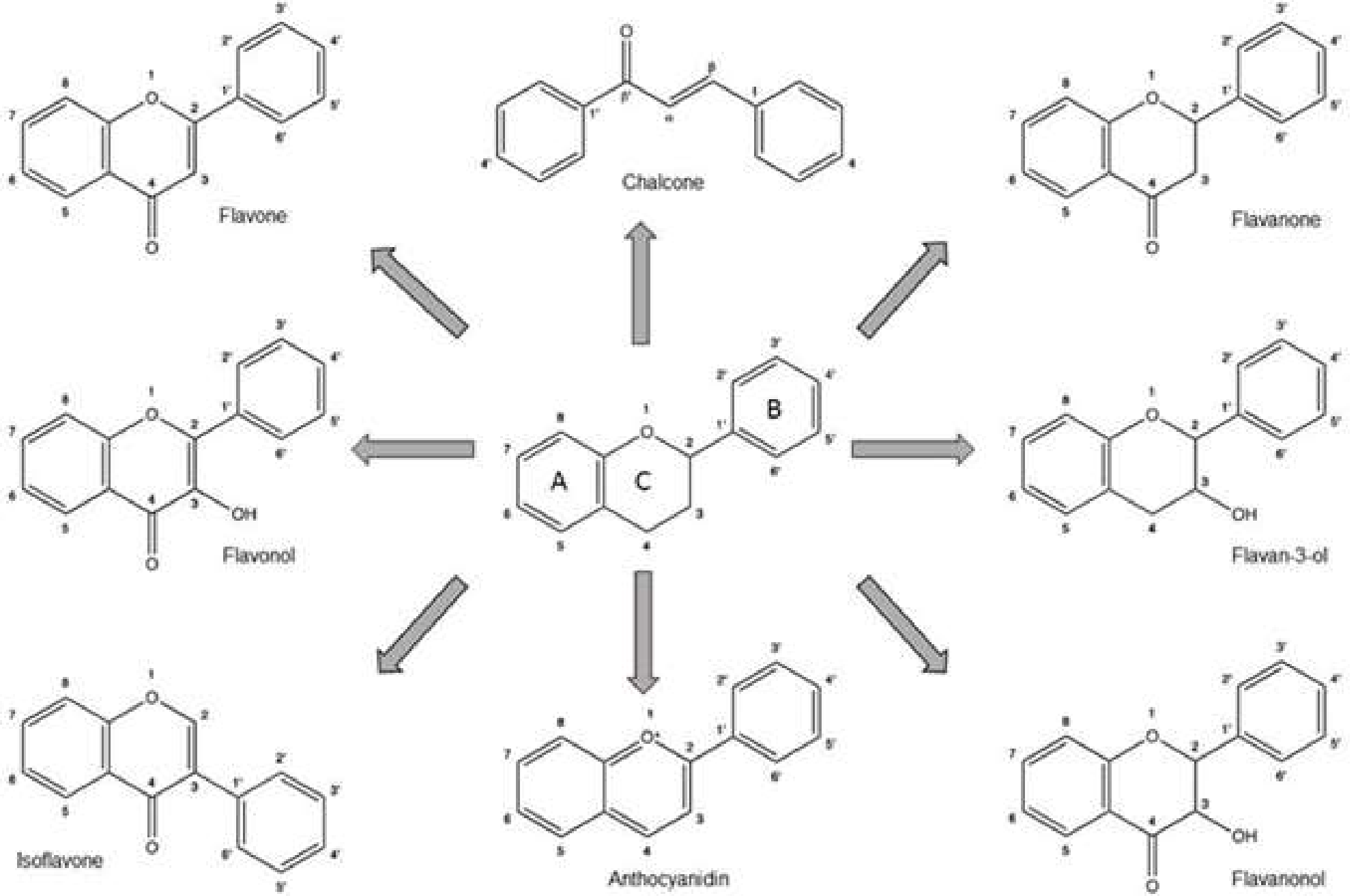
PROF. DRA. LILIANA MUSCHIETTI. CÁTEDRA DE FARMACOGNOSIA. FACULTAD DE FARMACIA Y BIOQUÍMICA. UNIVERSIDAD DE BUENOS AIRES

FLAVONOIDES

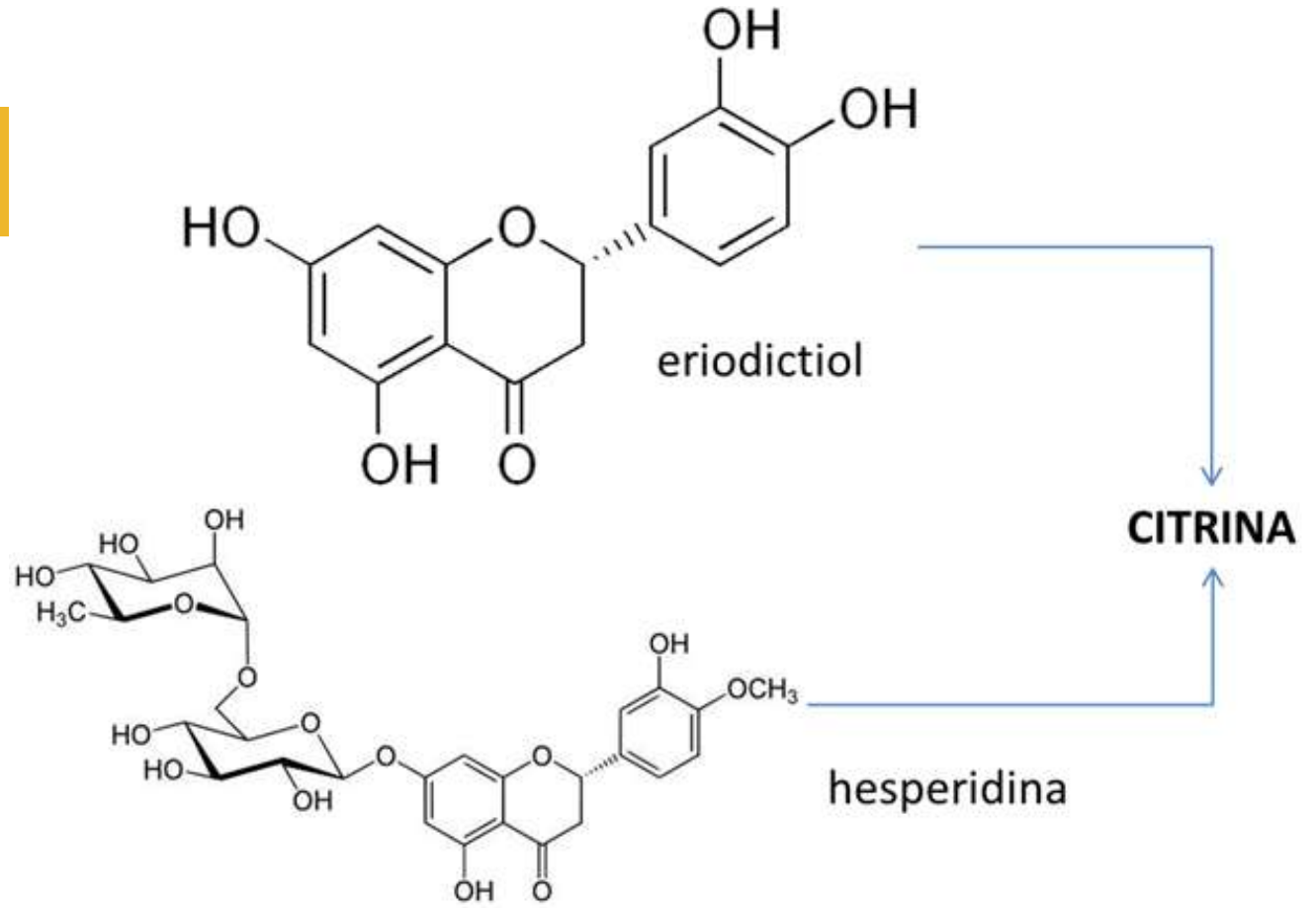


Estructura básica C6-C3-C6

CLASIFICACIÓN


Flavone
Chalcone
Flavanone
Flavonol
Flavan-3-ol
Isoflavone
Anthocyanidin
Flavanonol
A
B
C
OH

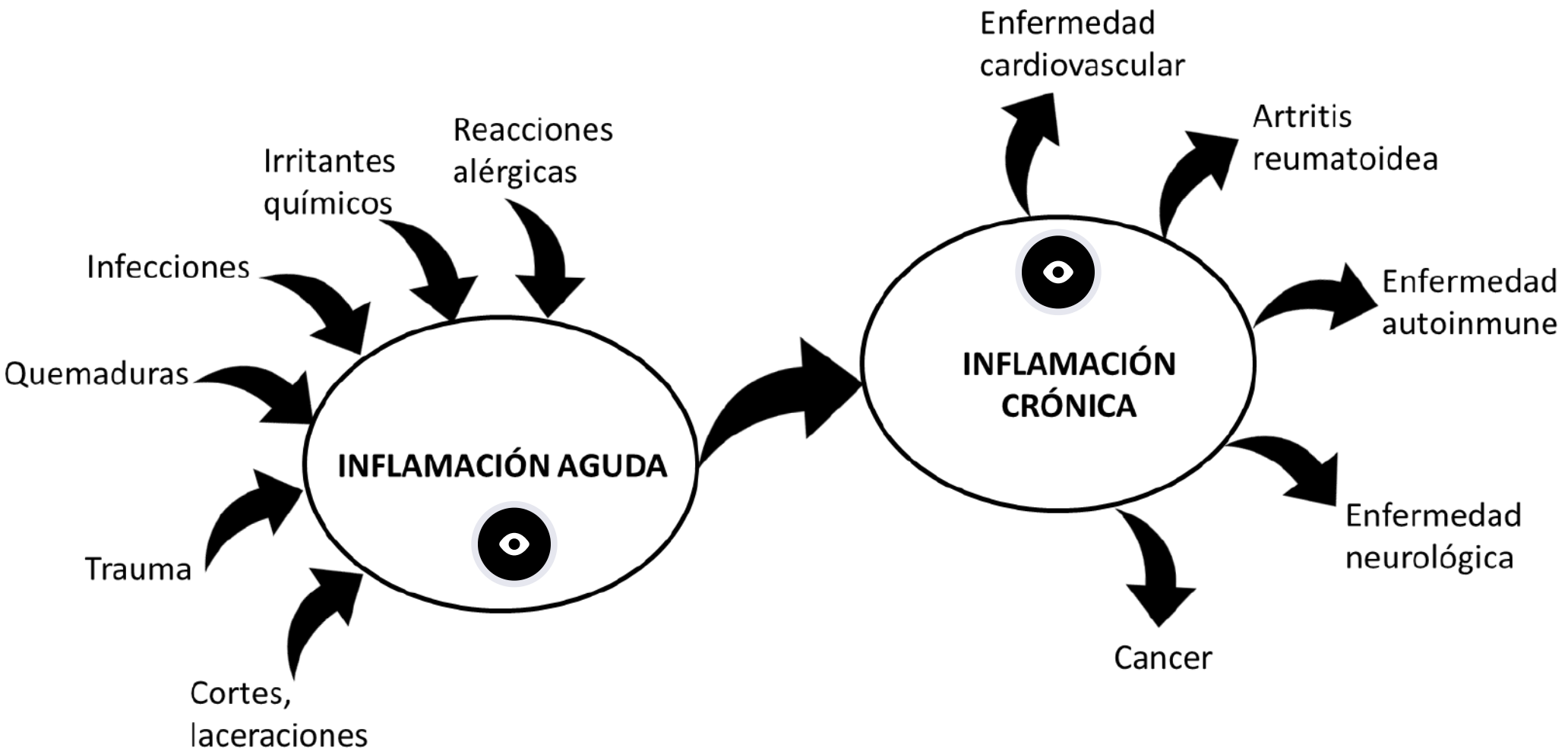
Actividad de “Vitamina P”



ACTIVIDADES BIOLÓGICAS

- Antioxidante
- Antiinflamatoria
- Hepatoprotectora
- Antibacteriana
- Antiviral
- Antidiabética
- Antiproliferativa
- Venotónica
- Vasculoprotectora

INFLAMACIÓN

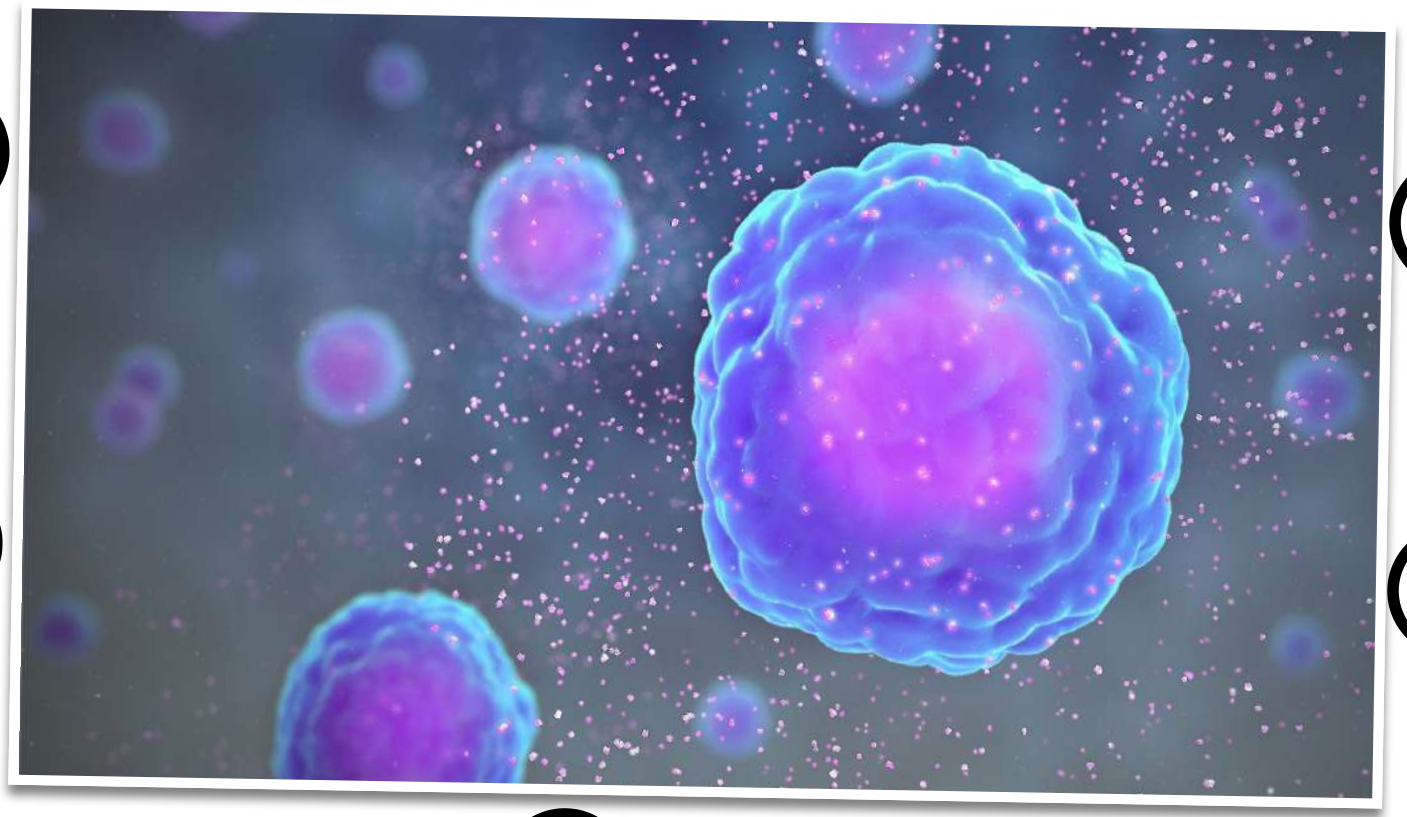


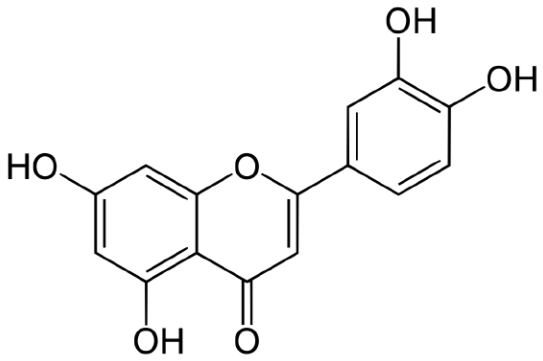
ACTIVIDAD ANTIINFLAMATORIA DE FLAVONOIDES

ACTIVIDAD	MECANISMO DE ACCIÓN	EFECTO
ACTIVIDAD ANTIOXIDANTE	Actividad atrapadora de radicales libres Inhibición de la producción de ROS Inhibición de enzimas pro-oxidantes	↓ Radicales libres ↓ Peroxidación lipídica
MODULACIÓN DE CÉLULAS INFLAMATORIAS	Modulación de la actividad enzimática Modulación de procesos secretorios	↓ Activación de células inflamatorias
MODULACIÓN DE ENZIMAS PROINFLAMATORIAS	Inhibición de enzimas del AA Inhibición de NOS	↓ Mediadores inflamatorios: NO, leucotrienos, PGs
MODULACIÓN DE MEDIADORES PROINFLAMATORIOS	Modulación en la producción de citoquinas	↓ Citoquinas inflamatorias: Interleuquinas, TNF-α
MODULACIÓN EN LA EXPRESIÓN DE GENES PROINFLAMATORIOS	Modulación en la transducción de señales	↓ Transcripción de genes proinflamatorios

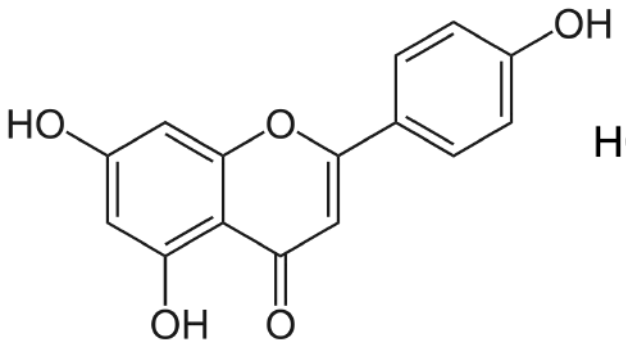
García-La Fuente et al. (2009). Inflamm. Res. 58:537-552

CITOQUINAS PROINFLAMATORIAS

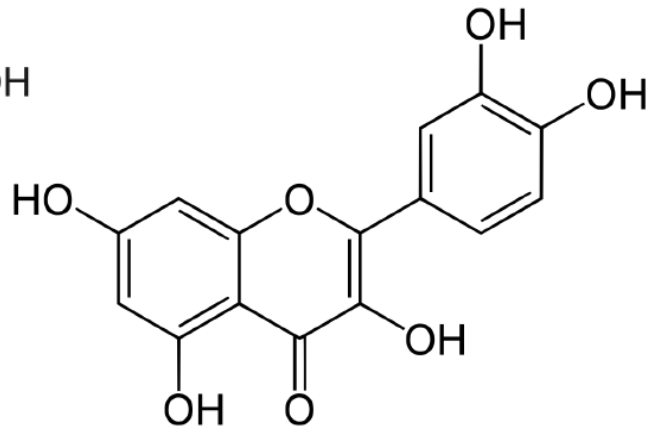




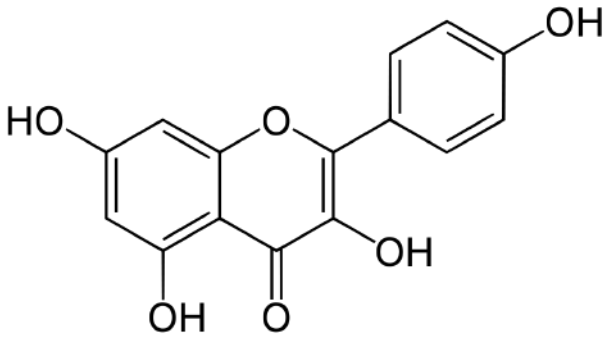
Luteolin



Apigenin



Quercetin



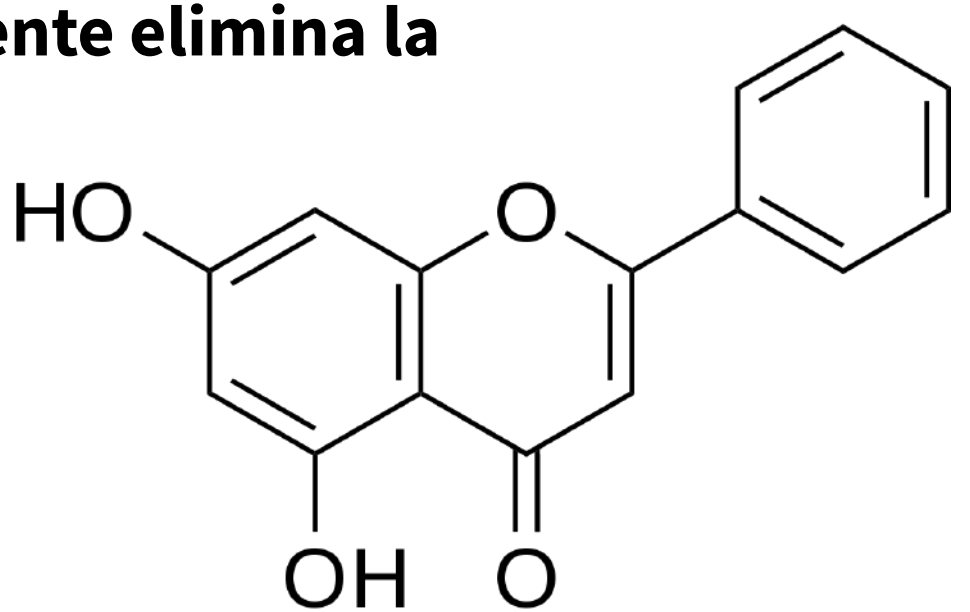
Kaempferol

1

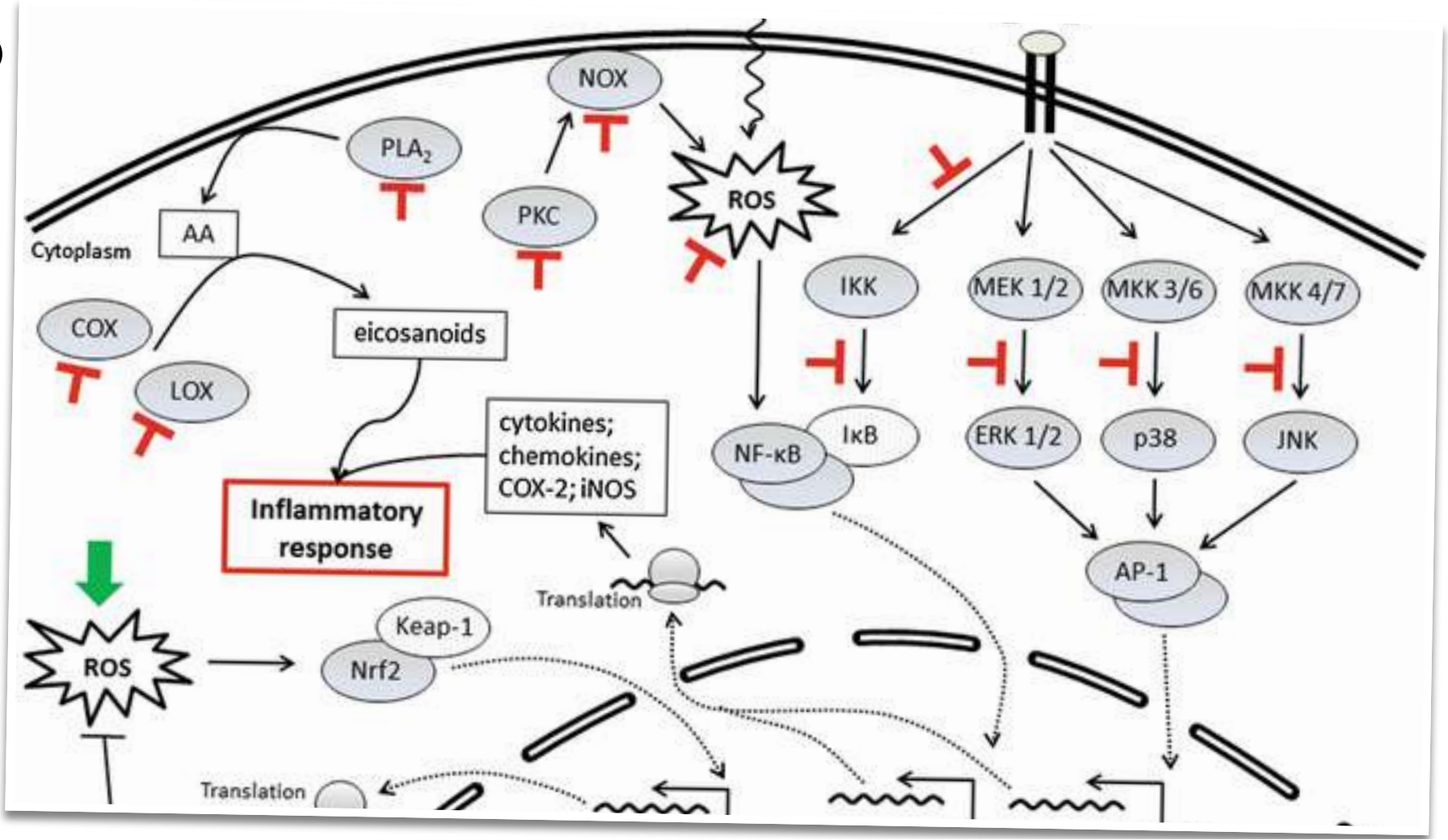
2

3

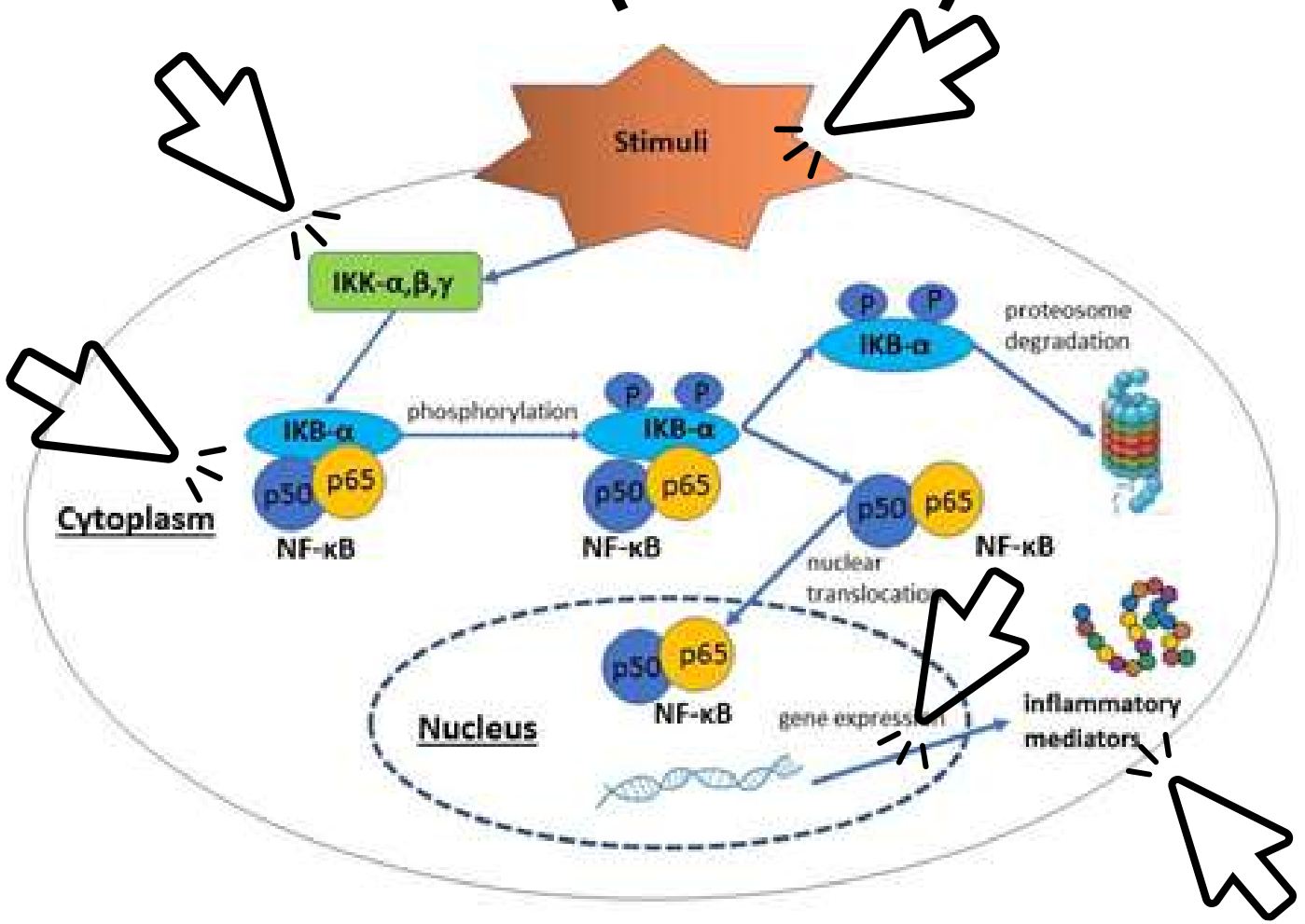
- **Sistema planar**
- **Insaturación (anillo C) C2-C3**
- **Número y posición de grupos OH en anillos A y B (particularmente C5, C7 , C3´ y C4´)**
- **Falta de OH en el anillo B aparentemente elimina la actividad**
- **Grupo ceto en posición 4 (anillo C)**



MODULACIÓN EN LA EXPRESIÓN DE GENES PROINFLAMATORIOS

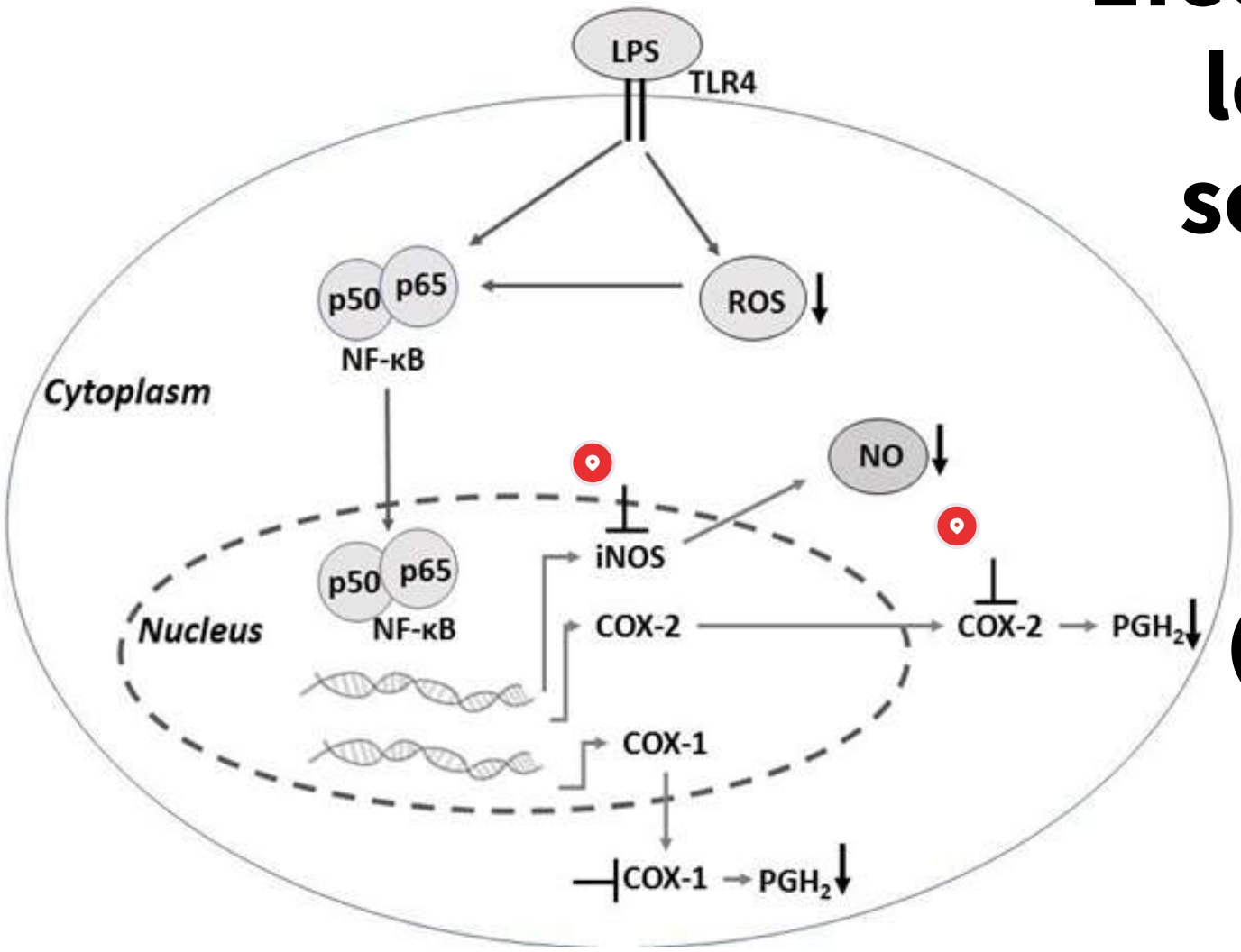


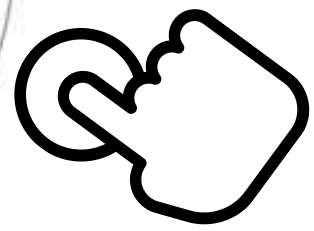
Factor de Transcripción Nuclear kappa-B (NF-kB)



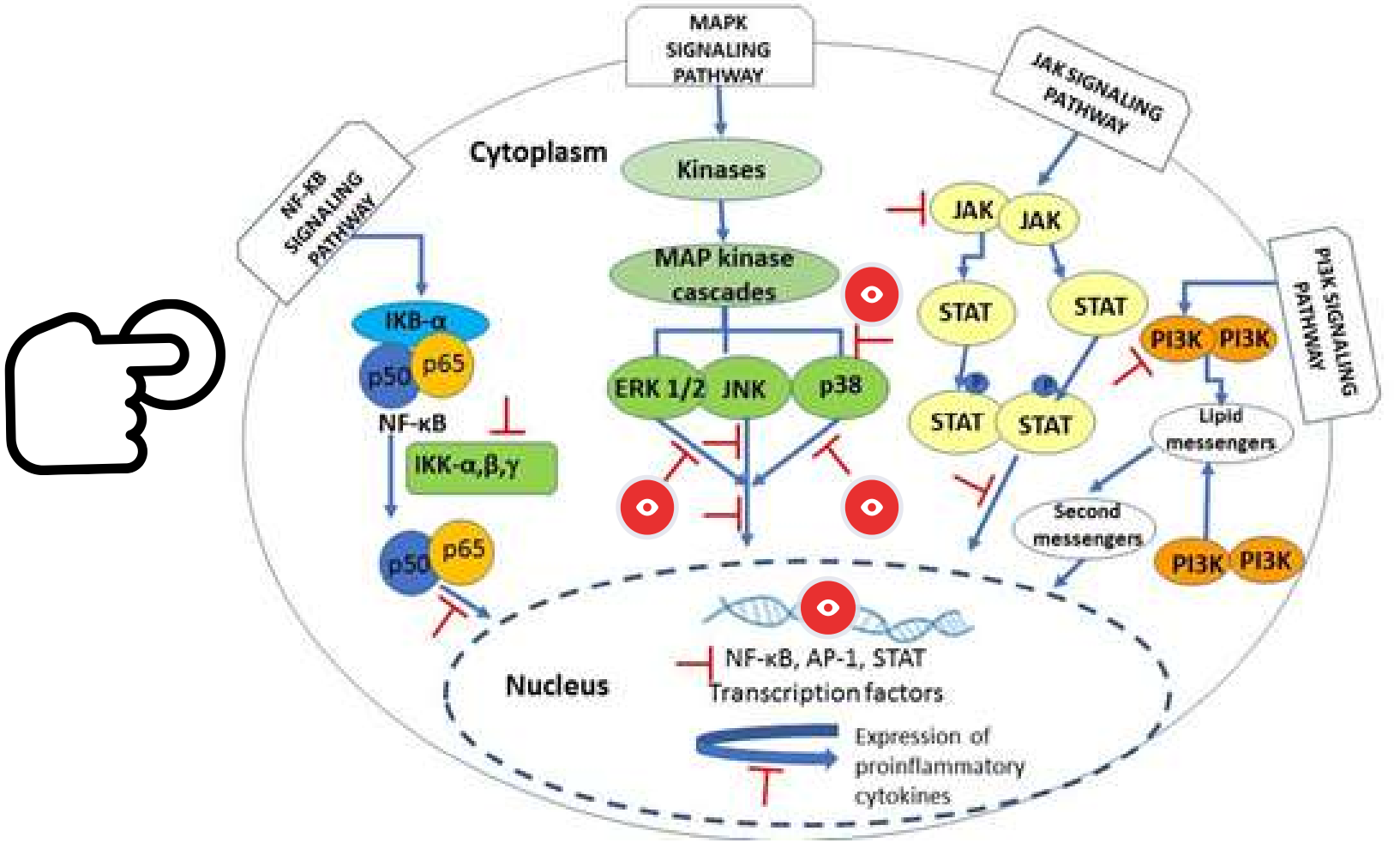
Muschietti L, Ulloa J, Redko F (2018). The role of flavonoids as modulators of inflammation and on cell signaling pathways. En: Natural Products as Source of Molecules with Therapeutic Potential: Research & Development, Challenges and Perspectives. Springer Nature Switzerland, pp 159-208.

Efecto inhibitorio de los flavonoides sobre ROS, NO y PGs



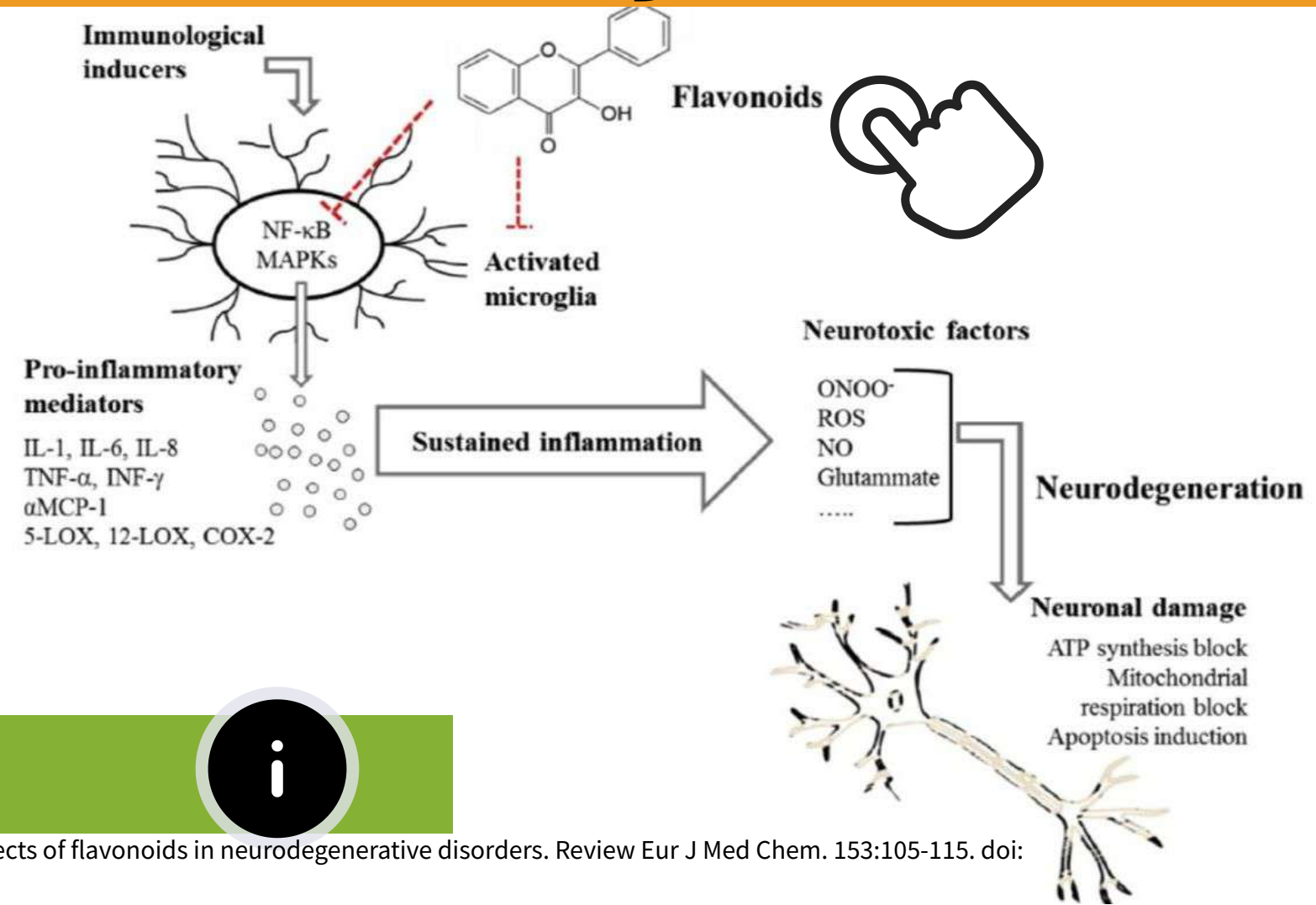


MECANISMO DE ACCIÓN POR EL CUAL LOS FLAVONOIDES BLOQUEAN LA INFLAMACIÓN A TRAVÉS DE LA INHIBICIÓN DE DIFERENTES VÍAS DE SEÑALIZACIÓN



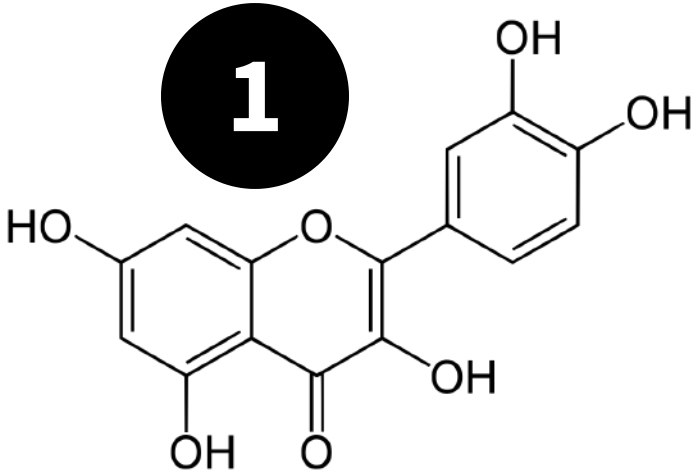
Muschietti L, Ulloa J, Redko F (2018). The role of flavonoids as modulators of inflammation and on cell signaling pathways. En: Natural Products as Source of Molecules with Therapeutic Potential: Research & Development, Challenges and Perspectives. Springer Nature Switzerland, pp 159-208.

Efecto anti-inflamatorio de los flavonoides en enfermedades neurodegenerativas



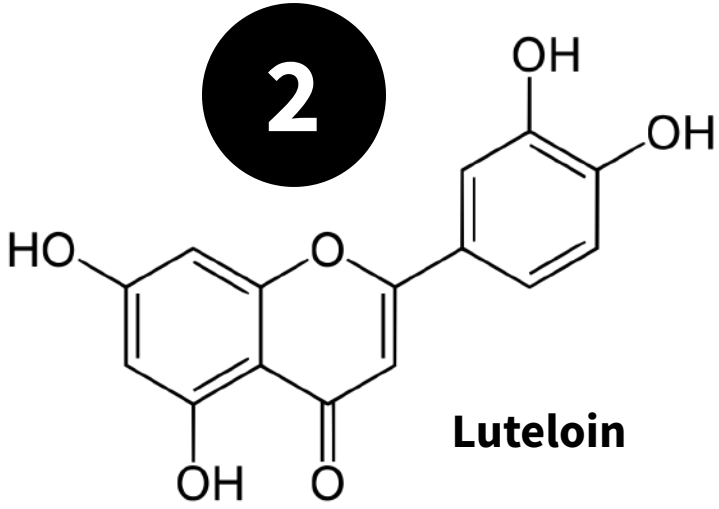
Carmela Spagnuolo et al. (2018). Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Review Eur J Med Chem. 153:105-115. doi: 10.1016/j.ejmech.2017.09.001

1



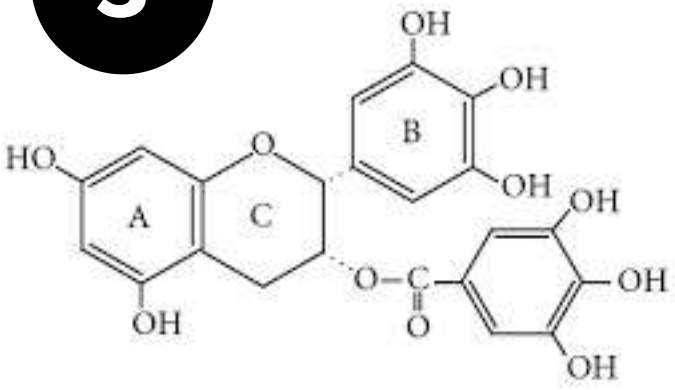
Quercetin

2

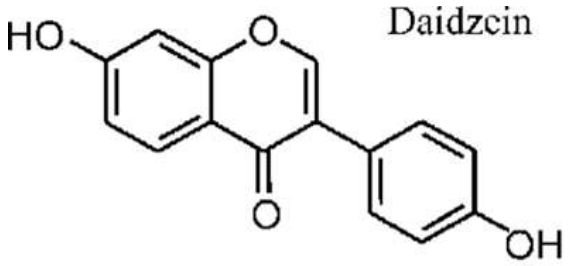


Luteloin

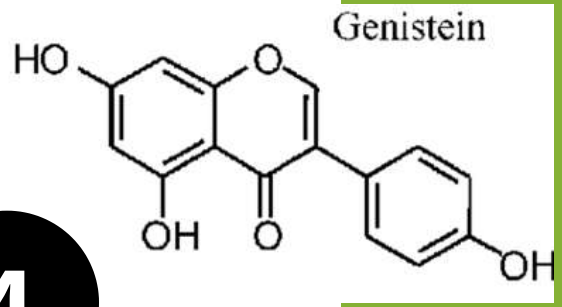
3



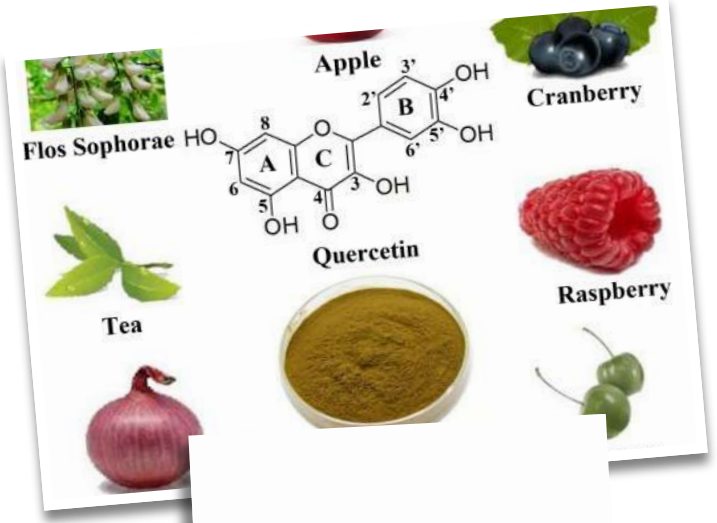
EGCG



4

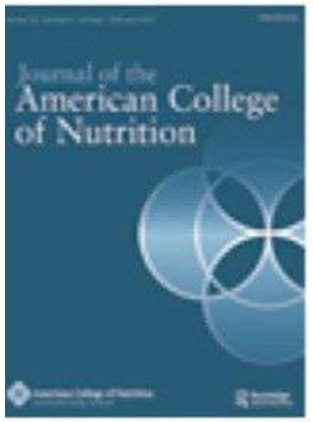


ENSAYOS CLÍNICOS



Quercetina

Hesperidina



Journal of the American College of Nutrition

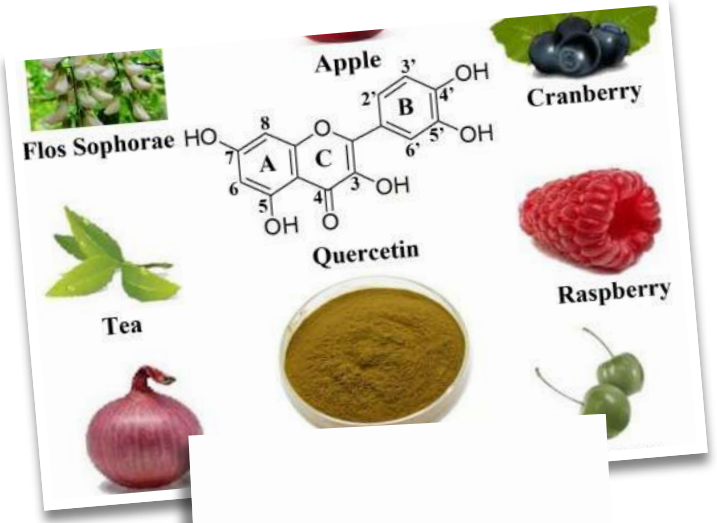
ISSN: 0731-5724 (Print) 1541-1087 (Online) Journal homepage: http://www.tandfonline.com/loi/uacn20

The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial

Fatemeh Javadi MSc, Arman Ahmadzadeh MD, Shahryar Eghtesadi PhD, Naheed Aryaeian PhD, Mozhdeh Zabihiyeganeh MD, Abbas Rahimi Foroushani PhD & Shima Jazayeri MD, PhD

To cite this article: Fatemeh Javadi MSc, Arman Ahmadzadeh MD, Shahryar Eghtesadi PhD, Naheed Aryaeian PhD, Mozhdeh Zabihiyeganeh MD, Abbas Rahimi Foroushani PhD & Shima Jazayeri MD, PhD (2016): The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial, Journal of the American College of Nutrition, DOI: 10.1080/07315724.2016.1140093

ENSAYOS CLÍNICOS



Quercetina

Hesperidina

Randomized Controlled Trial > J Clin Endocrinol Metab. 2011 May;96(5):E782-92.
doi: 10.1210/jc.2010-2879. Epub 2011 Feb 23.

Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome

Stefano Rizza [1], Ranganath Muniyappa, Micaela Iantorno, Jeong-a Kim, Hui Chen, Philomena Pullikotil, Nicoletta Senese, Manfredi Tesauro, Davide Lauro, Carmine Cardillo, Michael J Quon

Ensayos clínicos de medicamentos herbarios

Pycnogenol®
(Horphag Research Ltd, Switzerland)

Extract of *Pinus maritima*
Mixture of flavonoids, mainly procyanidins

Randomized Controlled Trial > Phytother Res. 2008 Aug;22(8):1087-92. doi: 10.1002/ptr.2461.

Effect of pine bark extract (Pycnogenol) on symptoms of knee osteoarthritis

Peter Cisár [1], Richard Jány, Iweta Waczulíková, Katarína Sumegová, Jana Muchová, Jozef Vojtassák, Zdenka Duračková, Miroslav Lisý, Peter Rohdewald

Affiliations expand

Observational Study > Minerva Endocrinol. 2019 Mar;44(1):97-101.
doi: 10.23736/S0391-1977.18.02820-1.

Pycnogenol®: supplementary management of symptomatic osteoarthritis with a patch. An observational registry study

Beatrice Feragalli [1 2], Mark Dugall [1 2], Roberta Luzzi [1 2], Andrea Ledda [1 2], Morio Hosoi [1 2], Gianni Belcaro [3 2], Maria R Cesarone [1 2]

ELSEVIER

Nutrition Research

Volume 27, Issue 11, November 2007, Pages 692-697

Research Article

Pycnogenol supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis ☆

Reza Farid [a], Zahra Mirfeizi [a], Mahyar Mirheidari [a], Zahra Rezaieyazdi [a], Hassan Mansouri [a], Habib Esmaelli [a], Sherma Zibadi [b], Peter Rohdewald [c], Ronald Ross Watson [b]

Randomized Controlled Trial > Redox Rep. 2008;13(6):271-6. doi: 10.1179/135100008X309019.

Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol

G Belcaro [1], M R Cesarone, S Errichi, C Zulli, B M Errichi, G Vinciguerra, A Ledda, A Di Renzo, S Stuard, M Dugall, L Pellegrini, G Gizzi, E Ippolito, A Ricci, M Cacchio, G Cipollone, I Ruffini, F Fano, M Hosoi, P Rohdewald

SILIMARINA

Livergol®, Goldaruo pharmaceutical

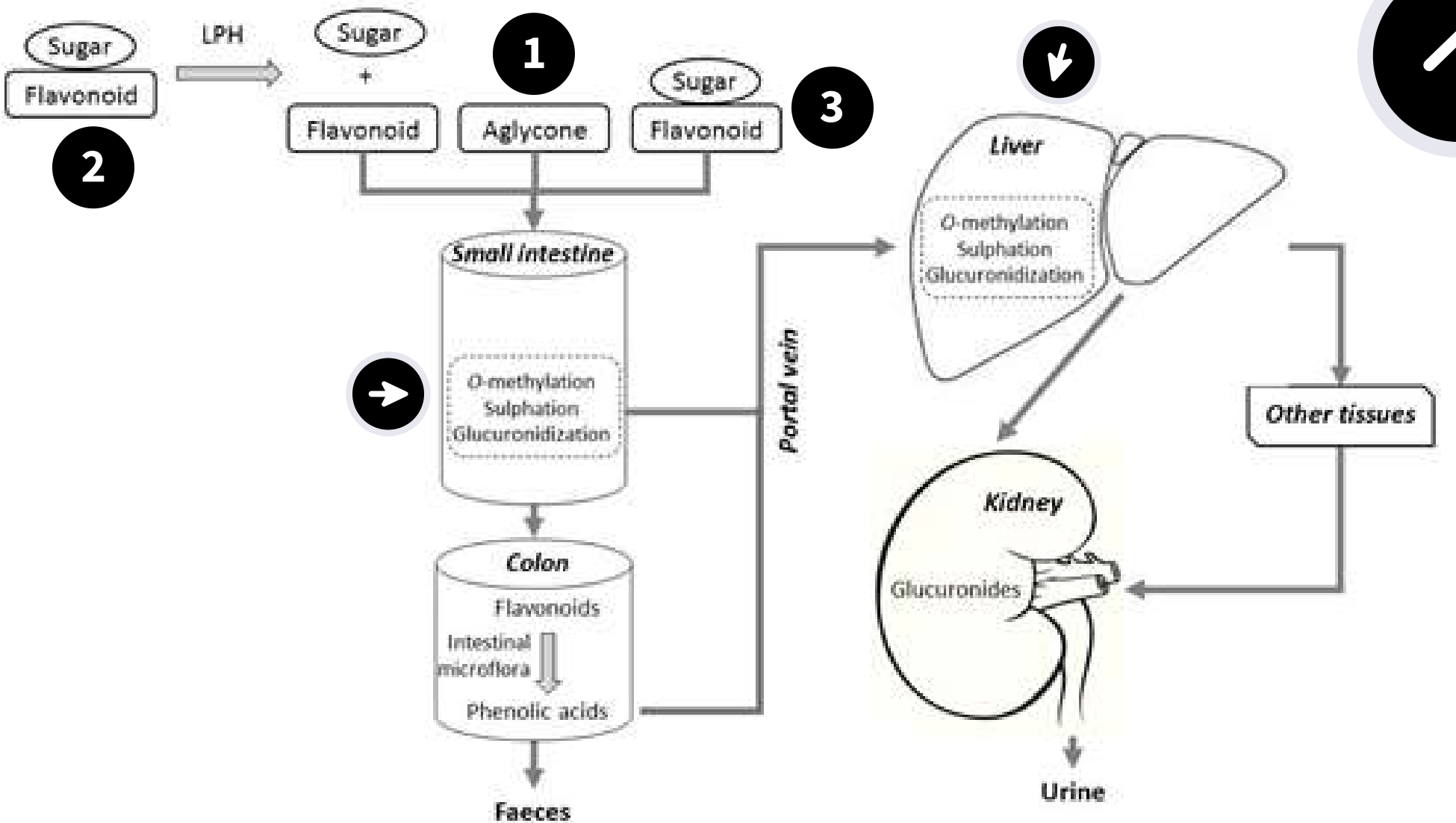
ENSAYO CLÍNICO

Se evaluaron los efectos de silimarina (Livergol®) sobre los marcadores inflamatorios en pacientes con artritris reumatoidea (AR)

Parámetros como la hinchazón, la sensibilidad y el dolor de las articulaciones se redujeron en pacientes con AR (420 mg/día, durante tres meses).

Shavandi M et al. Silymarin (Livergol®) Decreases Disease Activity Score in Patients with Rheumatoid Arthritis: A Non-randomized Single-arm Clinical Trial. Iran J Allergy Asthma Immunol. 2017 Apr;16(2):99-106. .

ABSORCIÓN Y METABOLISMO DE FLAVONOIDES



BIODISPONIBILIDAD DE FLAVONOIDES

BAJA SOLUBILIDAD EN AGUA → BAJA ABSORCIÓN

↓

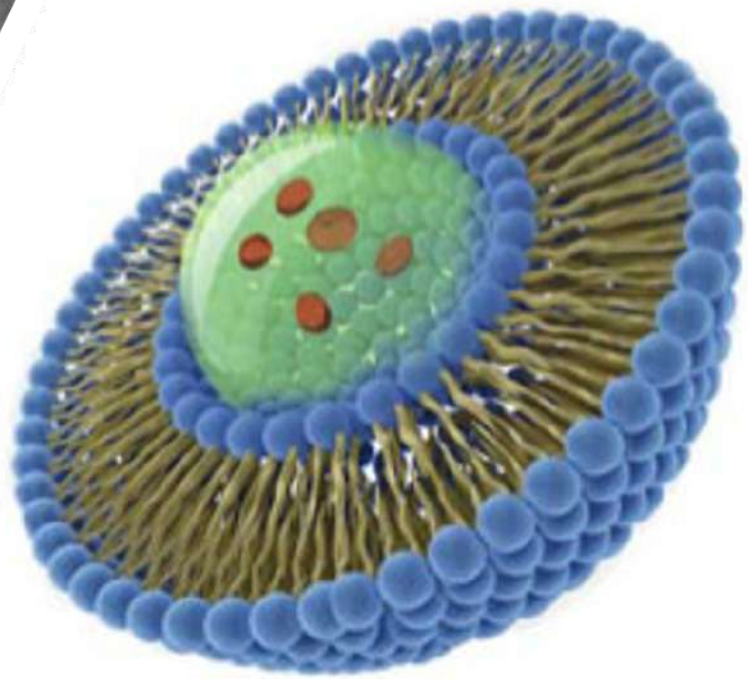
BAJA BIODISPONIBILIDAD (VÍA ORAL)

↓

FACTOR LIMITANTE

Estrategias

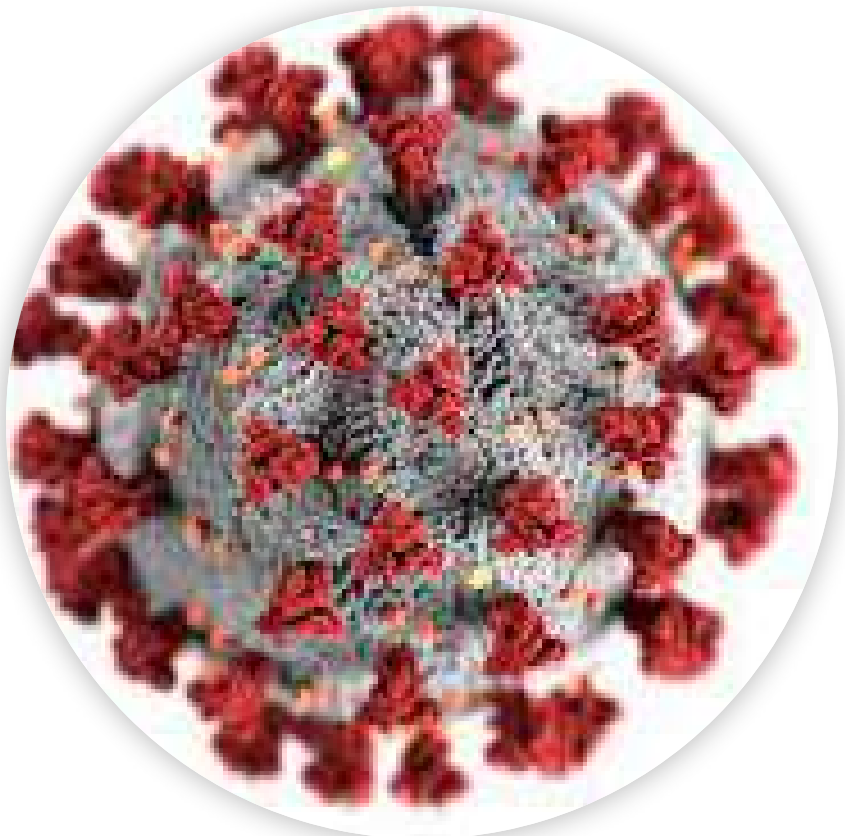
TECNOLOGÍAS FARMACÉUTICAS



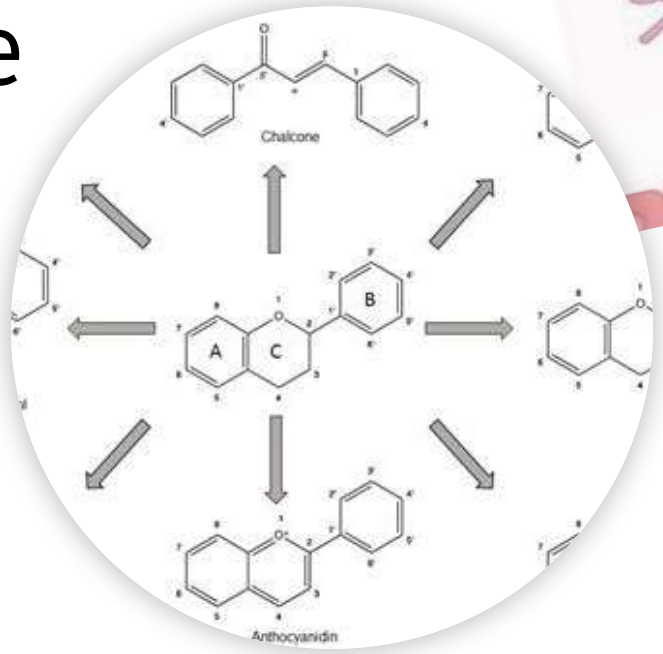
Rol potencial de los flavonoides en COVID-19

- La COVID-19 es una enfermedad infecciosa causada por el SARS-CoV-2.

- La infección puede causar un síndrome de dificultad respiratoria aguda asociada con una respuesta inmune sistémica e inflamación, afectando múltiples órganos que con frecuencia pueden conducir a un evento fatal.



Después de la infección viral es posible observar una respuesta inmunitaria del huésped y la producción de citoquinas inflamatorias



Tormenta de citoquinas

Review > Int J Mol Sci. 2020 Apr 28;21(9):3104. doi: 10.3390/ijms21093104.

Functional Role of Dietary Intervention to Improve the Outcome of COVID-19: A Hypothesis of Work

Giovanni Messina [1], Rita Polito [1], Vincenzo Monda [2], Luigi Cipolloni [1], Nunzio Di Nunno [3], Giulio Di Mizio [4], Paolo Murabito [5], Marco Carotenuto [6], Antonietta Messina [2], Daniela Pisanelli [1], Anna Valenzano [1], Giuseppe Cibelli [1], Alessia Scarinci [7], Marcellino Monda [2], Francesco Sessa [1]

International Journal of *Molecular Sciences*

MDPI

Review

Protective Effect of Epigallocatechin-3-Gallate (EGCG) in Diseases with Uncontrolled Immune Activation: Could Such a Scenario Be Helpful to Counteract COVID-19?

Marta Menegazzi [1,*], Rachele Campagnari [1], Mariarita Bertoldi [1], Rosalia Crupi [2], Rosanna Di Paola [3] and Salvatore Cuzzocrea [3,4]

Comment > Phytother Res. 2020 Dec;34(12):3085-3088. doi: 10.1002/ptr.6886. Epub 2020 Sep 30.

Molecular and functional resemblance of dexamethasone and quercetin: A paradigm worth exploring in dexamethasone-nonresponsive COVID-19 patients

Anil Pawar [1], Amit Pal [2]

Received: 6 April 2020 | Accepted: 7 April 2020
DOI: 10.1002/biof.1633

HYPOTHESIS

Biofactors WILEY

COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin

Theoharis C. Theoharides[1,2,3]

> J Inflamm (Lond). 2021 Jan 28;18(1):3. doi: 10.1186/s12950-021-00268-6.

Anti-inflammatory potential of Quercetin in COVID-19 treatment

Ali Saeedi-Boroujeni [1 2 3], Mohammad-Reza Mahmoudian-Sani [4]

Affiliations + expand

PMID: 33509217 PMCID: PMC7840793 DOI: 10.1186/s12950-021-00268-6

Phytomedicine. 2021 May; 85: 153315.
Published online 2020 Sep 9. doi: 10.1016/j.phymed.2020.153315

PMCID: PMC7480398
PMID: 32978039

Systems pharmacological study illustrates the immune regulation, anti-infection, anti-inflammation, and multi-organ protection mechanism of Qing-Fei-Pai-Du decoction in the treatment of COVID-19

Jing Zhao,[a,#] Saisai Tian,[b,#] Dong Lu,[a] Jian Yang,[b] Huawu Zeng,[b] Feng Zhang,[a] Dongzhu Tu,[a] Guangbo Ge,[a] Yuejuan Zheng,[c] Ting Shi,[c] Xin Xu,[d] Shiyi Zhao,[d] Yili Yang,[d] and Weidong Zhang[a,b,*]

U.S. National Library of Medicine

ClinicalTrials.gov

Showing: 1-14 of **14** studies 25 studies per page

Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	Trial to Study the Adjuvant Benefits of **Quercetin** Phytosome in Patients With **COVID-19**	• **COVID-19**	• Drug: Standard COVID-19 care • Dietary Supplement: **Quercetin** Phytosome	• Liaquat University Hospital Jāmshoro, Sindh, Pakistan
2	☐	Completed	Effect of **Quercetin** on Prophylaxis and Treatment of **COVID-19**	• **COVID-19**	• Dietary Supplement: **Quercetin** Prophylaxis • Dietary Supplement: **Quercetin** Treatment	• Kanuni Sultan Suleyman Training and Research Hospital Istanbul, Turkey
3	☐	Completed	Study to Investigate the Clinical Benefits of Dietary Supplement **Quercetin** for Managing Early Mild Symptoms of **COVID-19**	• **COVID-19**	• Drug: standard of care for COVID-19 as per the hospital guidelines • Dietary Supplement: **Quercetin** Phytosome (QP)	• King Edward Medical University Teaching Hospital Lahore, Punjab, Pakistan
4	☐	Unknown †	The Study of Quadruple Therapy Zinc, **Quercetin**, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With **COVID-19**	• **Covid-19**	• Drug: **Quercetin** • Dietary Supplement: bromelain	• Ministry of health.First health cluster ,Riaydh Riyadh, Saudi Arabia

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
5	☐	Completed	**Quercetin** in the Prevention of **Covid-19** Infection	• **Covid19**	• Dietary Supplement: **Quercetin** • Combination Product: Placebo	• Mariangela Rondanelli Pavia, Italy
6	☐	Completed	Nutritional Supplementation of Flavonoids **Quercetin** and Curcumin for Early Mild Symptoms of **COVID-19**	• **COVID-19**	• Drug: Standard of care • Dietary Supplement: Investigational treatment	• King Edward Medical University Teaching Hospital Lahore, Punjab, Pakistan
7	☐	Completed	Oral Curcumin, **Quercetin** and Vitamin D3 Supplements for Mild to Moderate Symptoms of **COVID-19**	• **Covid-19**	• Dietary Supplement: Complementary therapy • Drug: Standard of care	• Liaquat University Hospital Jāmshoro, Sindh, Pakistan
8	☐	Recruiting	Masitinib Combined With Isoquercetin and Best Supportive Care in Hospitalized Patients With Moderate and Severe **COVID-19**	• **SARS-CoV 2** • **COVID-19** • **Coronavirus Disease 2019**	• Drug: Masitinib • Drug: Isoquercetin • Drug: Best Supportive Care	• Centre Hospitalier du Pays d'Aix Aix-en-Provence, France • Le Tripode, Groupe hospitalier Pellegrin CHU de Bordeaux Bordeaux, France • CHU Clermont-

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
9	☐	Completed	The Effectiveness of Phytotherapy in **SARS-COV2(COVID-19)**	• a Randomized Double-blind Study • **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)** • PHYTOTHERAPIE	• Drug: **Quercetin**	• Riadh Boukef Sahloul, Sousse, Tunisia
10	☐	Completed	Efficacy of Psidii Guava's Extract For **COVID-19**	• **Covid19**	• Drug: Extract Psidii guava • Combination Product: Standard therapy for Covid-19 patient	• Faculty of Medicine, Baiturrahmah University Padang, West Sumatera, Indonesia
11	☐	Withdrawn	Safety and Efficacy of Hydroxychloroquine for the Treatment & Prevention of **Coronavirus Disease 2019 (COVID-19)** Caused by **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**	• **Covid19** • SARS (Severe Acute Respiratory Syndrome)	• Drug: Hydroxychloroquine • Dietary Supplement: Vitamins and Minerals • Drug: Azithromycin	
12	☐	Not yet recruiting	Study of Isoquercetin (IQC-950AN) Plus Standard of Care Versus Standard of Care Only for the Treatment of **COVID-19**	• **COVID-19**	• Drug: Isoquercetin (IQC-950AN)	

Clinical Trial > Int J Gen Med. 2021 Jun 8;14:2359-2366. doi: 10.2147/IJGM.S318720. eCollection 2021.

Possible Therapeutic Effects of Adjuvant Quercetin Supplementation Against Early-Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study

Francesco Di Pierro [1 2], Giuseppe Derosa [3 4], Pamela Maffioli [4], Alexander Bertuccioli [5], Stefano Togni [6], Antonella Riva [6], Pietro Allegrini [6], Amjad Khan [7 8], Saeed Khan [9], Bilal Ahmad Khan [9], Naireen Altaf [9], Maria Zahid [9], Ikram Din Ujjan [10], Roohi Nigar [11], Mehwish Imam Khushk [10], Maryam Phulpoto [11], Amanullah Lail [12], Bikha Ram Devrajani [13], Sagheer Ahmed [14]

Consideraciones Finales

- Una alta ingesta de flavonoides con la dieta se ha asociado con un menor riesgo de contraer diversas enfermedades.

- La actividad antiinflamatoria de los flavonoides implica, entre otros, la modulación de mediadores proinflamatorios a través de diferentes vías intracelulares que muestran una acción antiinflamatoria "multitarget".

- La mayoría de los estudios se llevan a cabo en ensayos in vitro o en modelos animales.

- Los estudios en humanos son escasos, pero proporcionan evidencia de la eficacia de los flavonoides como potenciales agentes antiinflamatorios.

- El factor más limitante de los flavonoides es la baja solubilidad en agua, lo que conduce a una menor absorción y en consecuencia, a una menor biodisponibilidad luego de la administración por v.o

- En este sentido, es necesario el desarrollo de nuevas tecnologías (nanotecnología, complejos de inclusión, dispersión sólida) para mejorar la biodisponibilidad de estos compuestos y aumentar su efectividad.

¡Muchas gracias!