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INTERACCIONES FÁRMACO-ALIMENTO

Mar Blanco Rogel

Julio 2021

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INTERACCIONES

FÁRMACO- ALIMENTO/NUTRIENTE

HISTORIA IMA

- Primera referencia en 1927
  - **Aceites minerales y vitaminas liposolubles**
- 1950: Isoniazida – vitamina B6
- 1965 (Asatoor, Blackwell):
  - **SINDROME DEL QUESO**

TRANILCIPROMINA
AMINAS BIOGENAS

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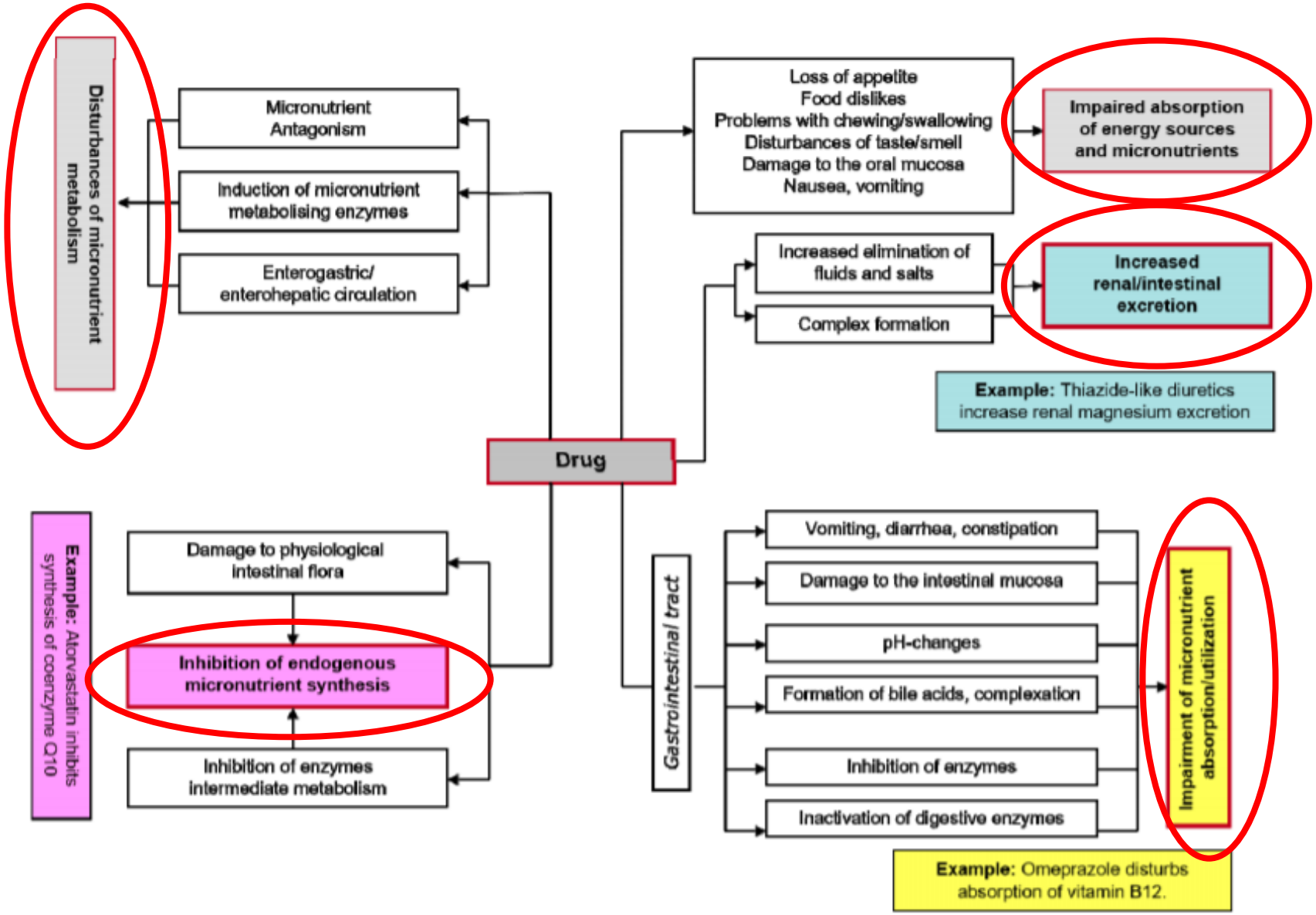
MECANISMO



Int. J. Mol. Sci. 2019, 20, 2094; doi:10.3390/ijms20092094

INTERACCIONES MEDICAMENTO-ALIMENTO FÁRMACO-NUTRIENTE

1. Disminución de la síntesis
2. Maldigestión o malabsorción
3. Alteración del metabolismo
4. Alteración de la eliminación

DISMINUCIÓN DE LA SÍNTESIS ENDÓGENA

NUTRIENTE	SÍNTESIS	FC QUE AFECTA SU SÍNTESIS
VITAMINA D	Piel	Agentes tópicos PABA
VITAMINA K	Bacterias intestinales	Antibióticos
BIOTINA	Bacterias intestinales	Antibióticos
Coenzima Q10	Endógena a partir del colesterol	Estatinas

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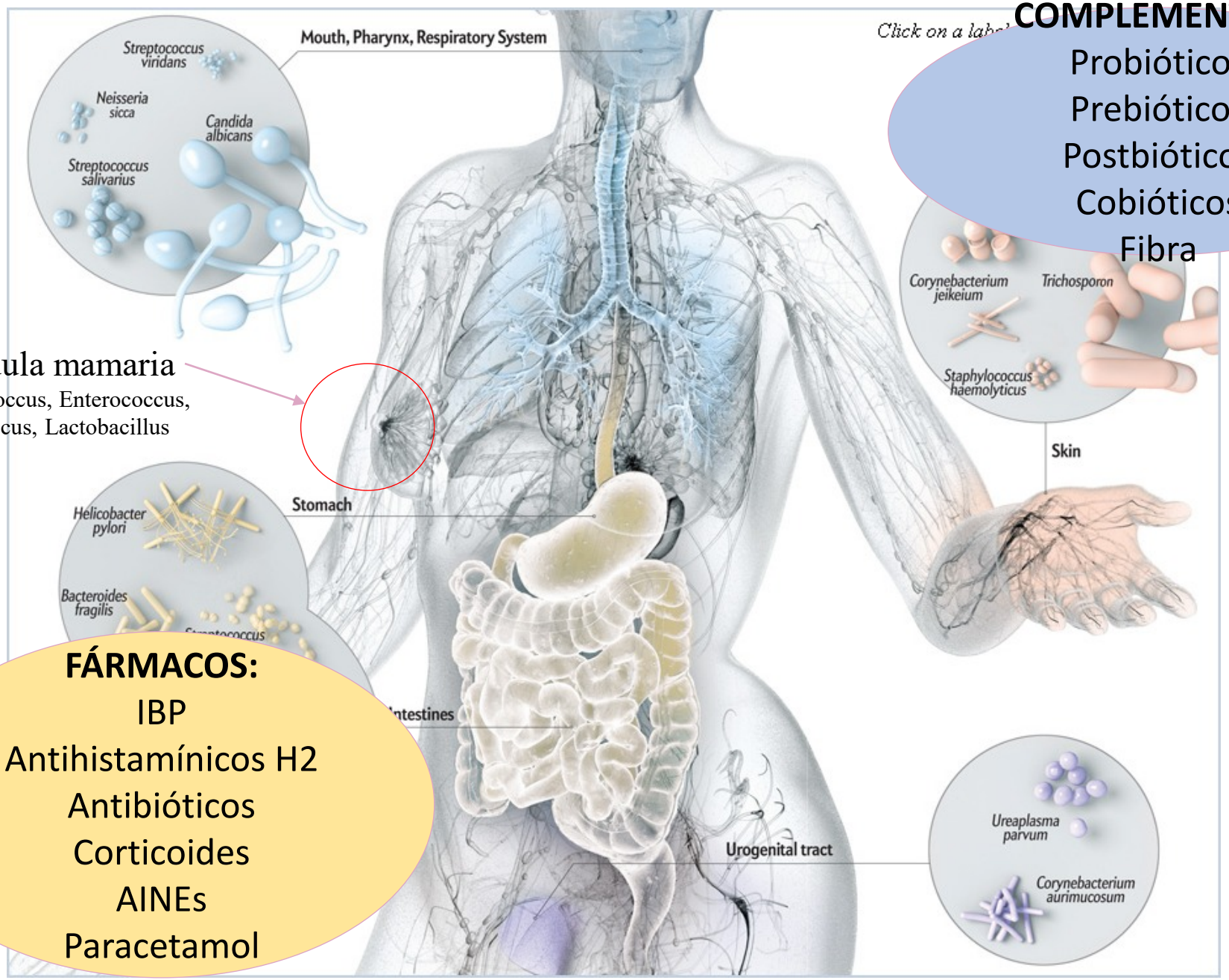
COMPLEMENTOS:

Probióticos
Prebióticos
Postbióticos
Cobióticos
Fibra



Glándula mamaria

Streptococcus, Enterococcus, Lactococcus, Lactobacillus

FÁRMACOS:

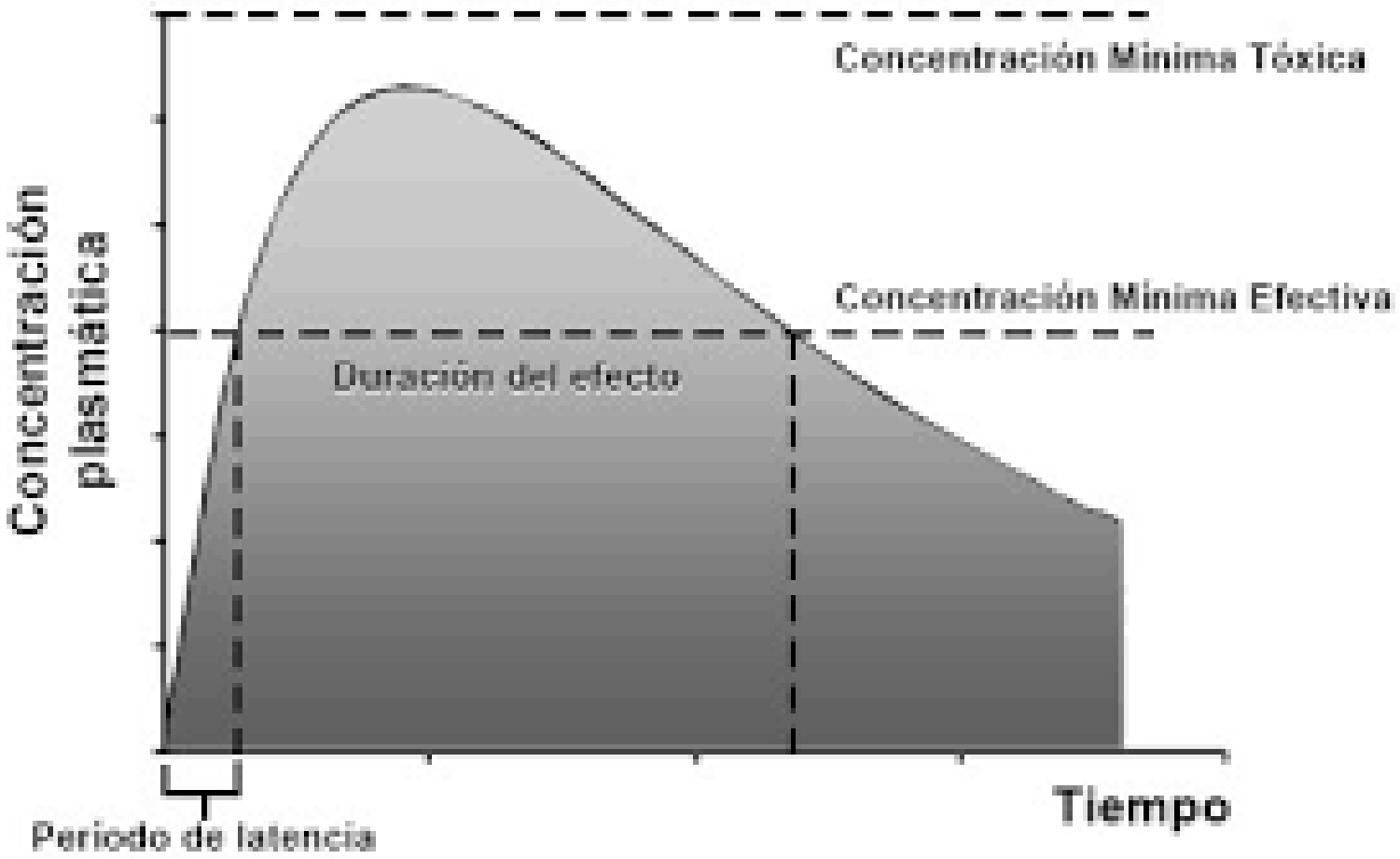
IBP
Antihistamínicos H2
Antibióticos
Corticoides
AINEs
Paracetamol

ANTIBIÓTICOS

ALTERACIONES MÁS FRECUENTES

- Afectación microbiota: Crecimiento de bacterias/levaduras oportunistas
- Diarrea
- Disminución de la síntesis de vit K y biotina
- IAM: tetraciclinas, ciprofloxacino, azitromicina

CURVAS NIVELES PLASMÁTICOS ANTIBIÓTICOS



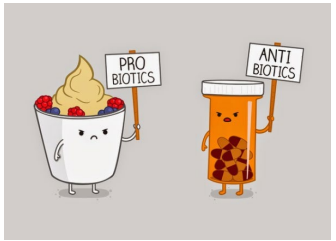
Microbiology (2010), 156, 3216–3223 DOI 10.1099/mic.0.040618-0

Mini-Review

Long-term impacts of antibiotic exposure on the human intestinal microbiota

Cecilia Jernberg,[1] Sonja Löfmark,[2] Charlotta Edlund[3,4] and Janet K. Jansson[5,6]

- **CLINDAMICINA**: 1.5-2 años
- **TRATAMIENTO PARA *H.pylori:*** hasta 4 años
- **AMOXICILINA**: hasta 60 días
- **AMOXICILINA-CLAVULÁNICO:** sin bifidobacterias hasta pasados los 14 días



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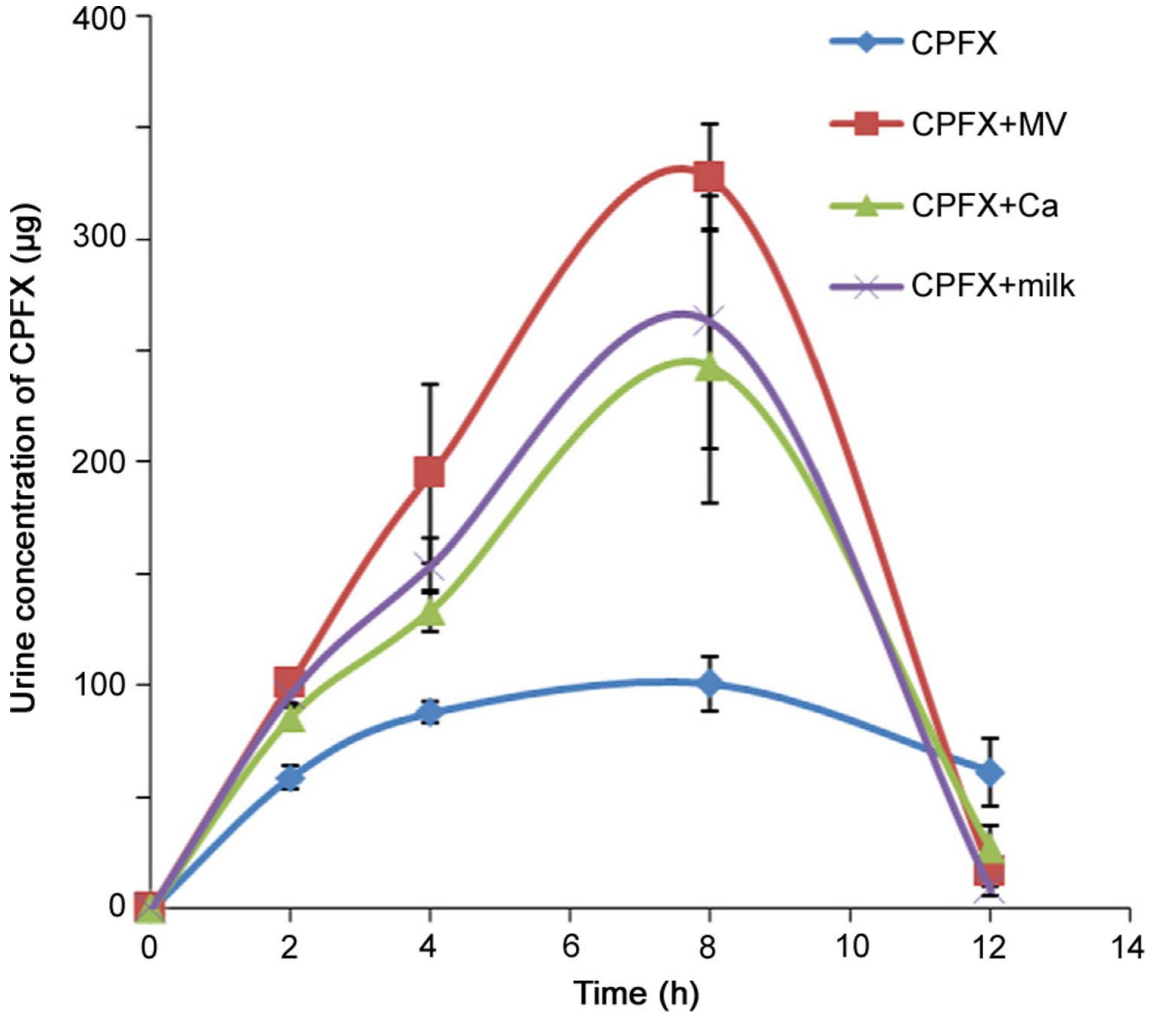
QUELACION



Dey B, Katakam P, Assaleh FH, Chandu BR, Adiki SK, Mitra A. *In vitro-in vivo* studies of the quantitative effect of calcium, multivitamins and milk on single dose ciprofloxacin bioavailability. J Pharm Anal. 2015 Dec;5(6):389-395.

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ARTICLE

doi:10.1038/nature25979

Extensive impact of non-antibiotic drugs on human gut bacteria

Lisa Maier[1]*, Mihaela Pruteanu[1]†*, Michael Kuhn[2]*, Georg Zeller[2], Anja Telzerow[1], Exene Erin Anderson[1], Ana Rita Brochado[1], Keith Conrad Fernandez[1], Hitomi Dose[3], Hirotada Mori[3], Kiran Raosaheb Patil[2], Peer Bork[2,4,5,6] & Athanasios Typas[1,2]

A few commonly used non-antibiotic drugs have recently been associated with changes in gut microbiome composition, but the extent of this phenomenon is unknown. Here, we screened more than 1,000 marketed drugs against 40 representative gut bacterial strains, and found that 24% of the drugs with human targets, including members of all therapeutic classes, inhibited the growth of at least one strain *in vitro*. Particular classes, such as the chemically diverse antipsychotics, were overrepresented in this group. The effects of human-targeted drugs on gut bacteria are reflected on their antibiotic-like side effects in humans and are concordant with existing human cohort studies. Susceptibility to antibiotics and human-targeted drugs correlates across bacterial species, suggesting common resistance mechanisms, which we verified for some drugs. The potential risk of non-antibiotics promoting antibiotic resistance warrants further exploration. Our results provide a resource for future research on drug–microbiome interactions, opening new paths for side effect control and drug repurposing, and broadening our view of antibiotic resistance.

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ARTICLE

doi:10.1038/nature25979

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Features of drugs with anticommensal activity

Drugs from all major ATC indication areas exhibited anticommensal activity, with antineoplastics, hormones and compounds that target the nervous system inhibiting gut bacteria more than other medications (Extended Data Figs 9a, 10). Three ATC subclasses (antimetabolites, antipsychotics and calcium-channel blockers) were significantly enriched in hits (Extended Data Fig. 9a). Antimetabolites are used as

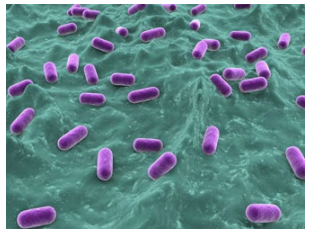
Many pharmaceuticals influence the human gut microbiota. As gut bacteria, in turn, can also modulate drug efficacy and toxicity[39], the emerging drug–microbe network could guide therapy and drug development. The resource described here opens up new avenues for translational applications in mitigating drug side effects, improving drug efficacy, repurposing of human-targeted drugs as antibacterials or microbiome modulators, and controlling antibiotic resistance (see Supplementary Discussion). However, before any translational application can be pursued, our *in vitro* findings need to be tested rigorously *in vivo* (in animal models, pharmacokinetic studies and clinical trials) and understood better mechanistically.

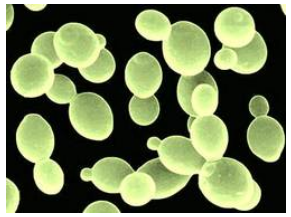
BACTERIAS VS LEVADURAS

TABLA 1. Diferencias principales entre levaduras y bacterias y sus implicaciones como probióticos[101]

	BACTERIA	*LEVADURA*	*CONSECUENCIA*
Presencia en la flora intestinal humana Tamaño célula Pared celular	99% 1 µm Peptidoglicano LPS (Gram-negativo) LTA (Gram-positivo)	<1% 10 µm Quitina, manosa (PPM, PLM) glucano	Impedimento esteárico Respuesta inmune a través de TLRs, receptores de lectinas
Condiciones de crecimiento óptimas: pH, temperatura (°C)	6,5 – 7,5 10-80	4,5 – 6,5 20-30	Diferentes lugares de acción en el tracto gastrointestinal
Resistencia a antibióticos	No	Sí	Eficacia en combinación con antibioticoterapia
Transmisión de material genético (p. ej., resistencia a los antibióticos)	Sí	No	

LPS = lipopolisacáridos; ALT = ácido lipoteicoico; FMP = fosfopeptidomanano; FLM = fosfolipomanano; RTT = receptor tipo Toll.





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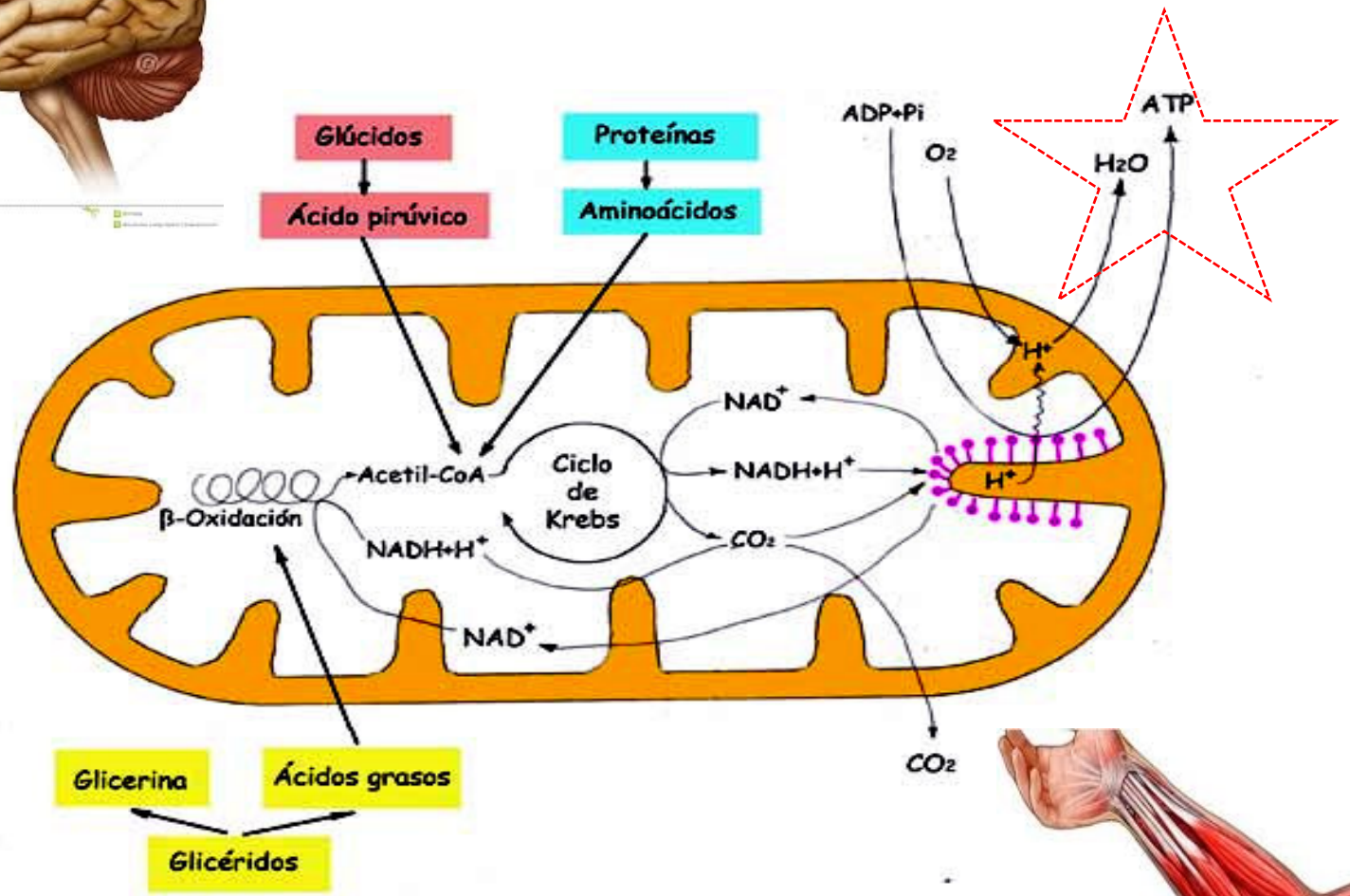
COENZIMA Q10

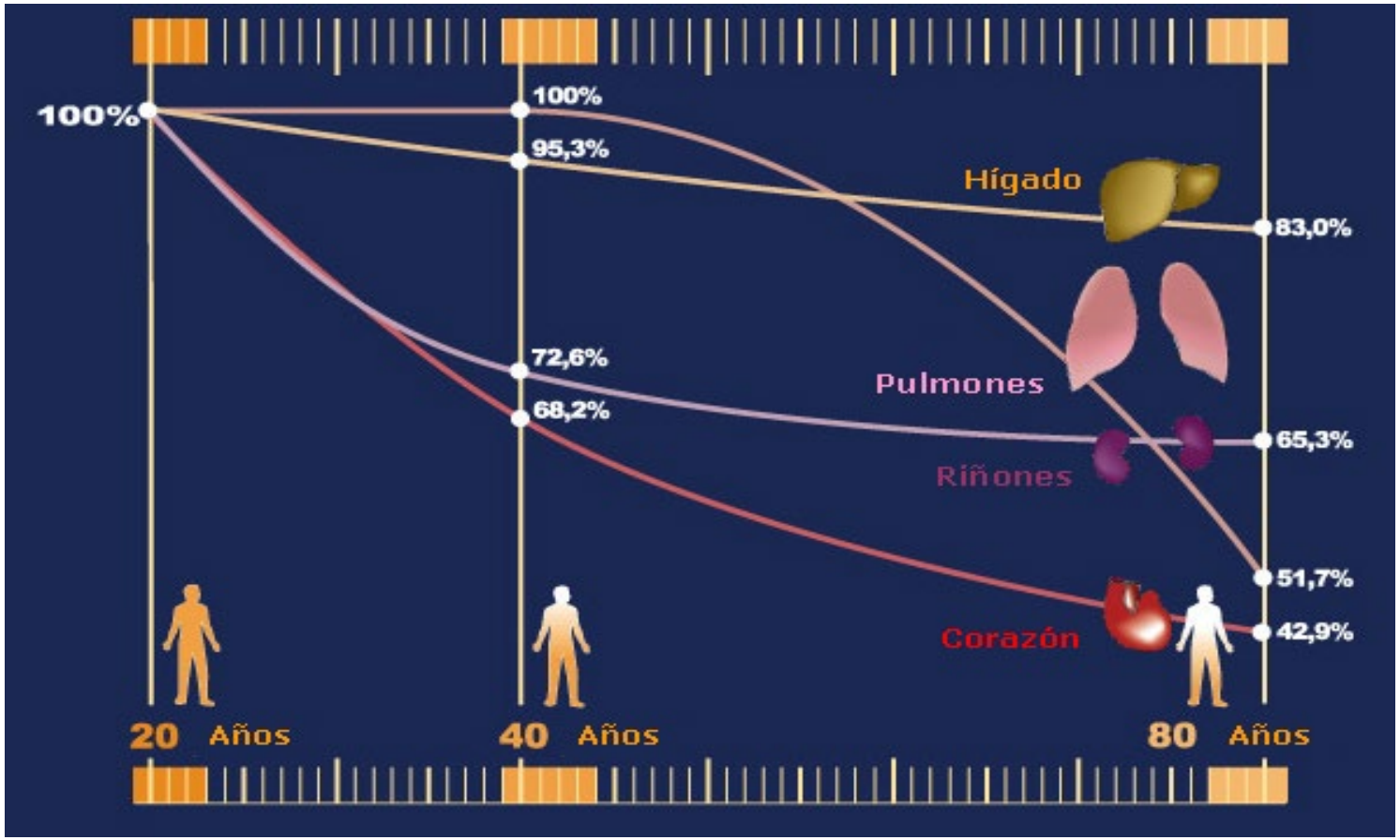


FÁRMACOS QUE REDUCEN LOS NIVELES DE CoQ10

- Orlistat[1]: reduce la absorción de CoQ10
- Beta bloqueantes[2]: disminuye la síntesis de CoQ10
- Biguanidas[3]: disminuye la síntesis de CoQ10
- Clondina[4]: disminuye la síntesis de CoQ10
- Gemfibrozilo[5]: reduce la absorción de CoQ10
- Haloperidol[6]: disminuye la síntesis de CoQ10
- Inhibidores de la HMG-CoA[7]: disminuye la síntesis de CoQ10
- Hidralazina[2]: disminuye la síntesis de CoQ10
- Metildopa [4] : disminuye la síntesis de CoQ10
- Fenotiazidas [6] : disminuye la síntesis de CoQ10
- Sulfonilureas [3]: disminuye la síntesis de CoQ10 (acetohexamida, gliburida, tolazamida).
- Diuréticos tiazídicos [4] : disminuye la síntesis de CoQ10
- Antidepresivos tricíclicos [6] : disminuye la síntesis de CoQ10

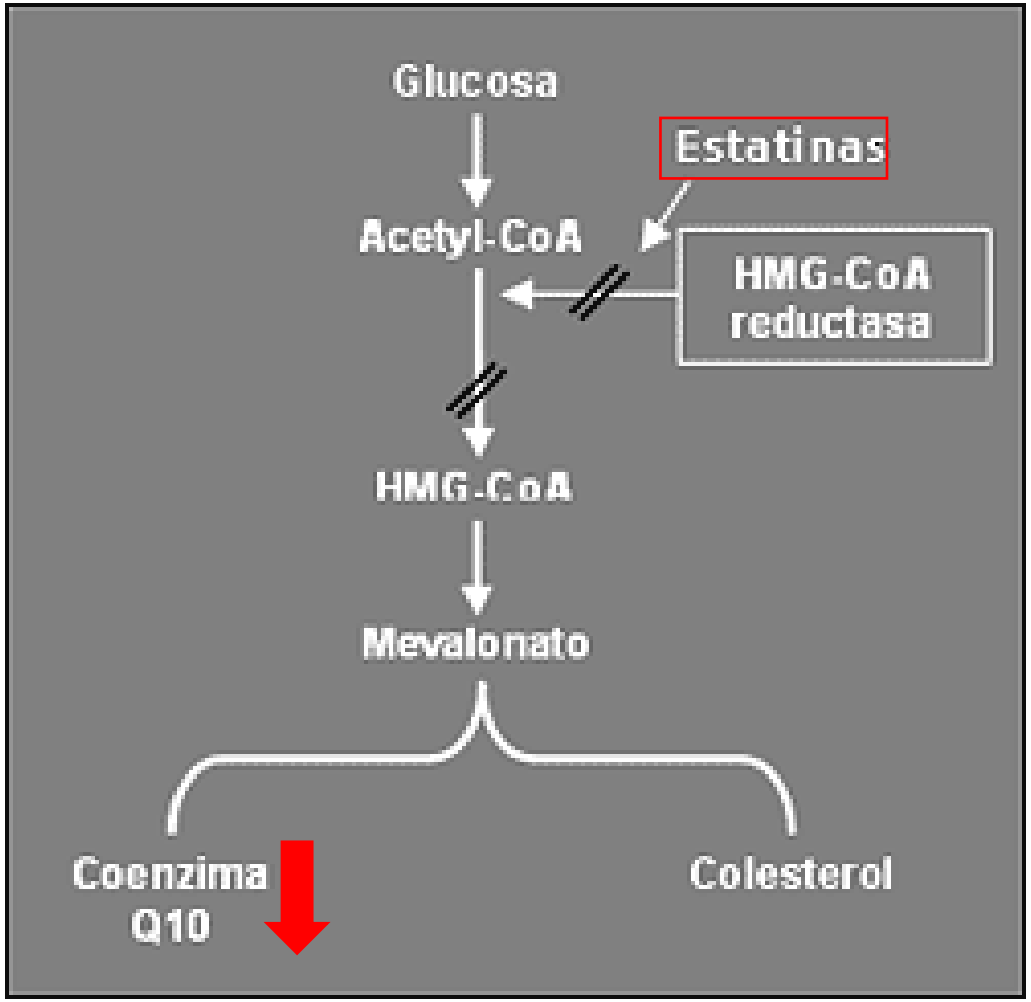
Xenical (orlistat), Product Prescribing Information. Nutley, NJ: Roche Laboratories, Inc., Sept 2000. 2,- Kishi T, et al. Bioenergetics in clinical medicine XV. Inhibition of coenzyme Q10-enzymes by clinically used adrenergic blockers of beta-receptors. Res Commun Chem Pathol Pharmacol. 1977;17(1):157-64. 3,- Kishi T, et al. K. Bioenergetics in clinical medicine XI. Studies on coenzyme Q and Diabetes Mellitus. J Med 976;7(3):307-21. 4,- Kishi H, et al. Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used anti-hypertensive drugs. Res Commun Chem Pathol Pharmacol 1975;12(3):533-40. 5.- Aberg F, et al. Gemfibrozil-induced decrease in serum Ubiquinone and alpha- and gamma-tocopherol levels in men with combined hyperlipidaemia. Eur J Clin Invest 1998;28(3):235-42. 6,- Kishi T, et al.- Inhibition of myocardial respiration by psychotherapeutic drugs and prevention by coenzyme Q10. In: Biomedical and clinical aspects of coenzyme Q10. Yamamura Y, Folkers K, Ito Y, editors. Vol 2. Amsterdam: Elsevier/North-Holland Biomedical Press; 1980. p. 139-54. 7,- Ghirlanda G, et al. Evidence of plasma Co10- lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol 1993;33(3):226-9.

CONCENTRACIÓN COQ10



[Kalen et al., Lipids, 24: 579,1989]

ESTATINAS



Estatinas/Pravastatina/atorvastatina/ lovastatina…

↑ dosis → ↑ efecto inhibidor

80 mg atorvastatina/30 días → ↓ CoQ10 52%

Causa de la miopatía?

Levadura de arroz rojo (*Monascus purpureus)*

(Watts et al., 1993; Ghirlanda et al., 1993; Bargossi et al., 1994; Mabuchi et al., 2005)

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EXPERT REVIEWS

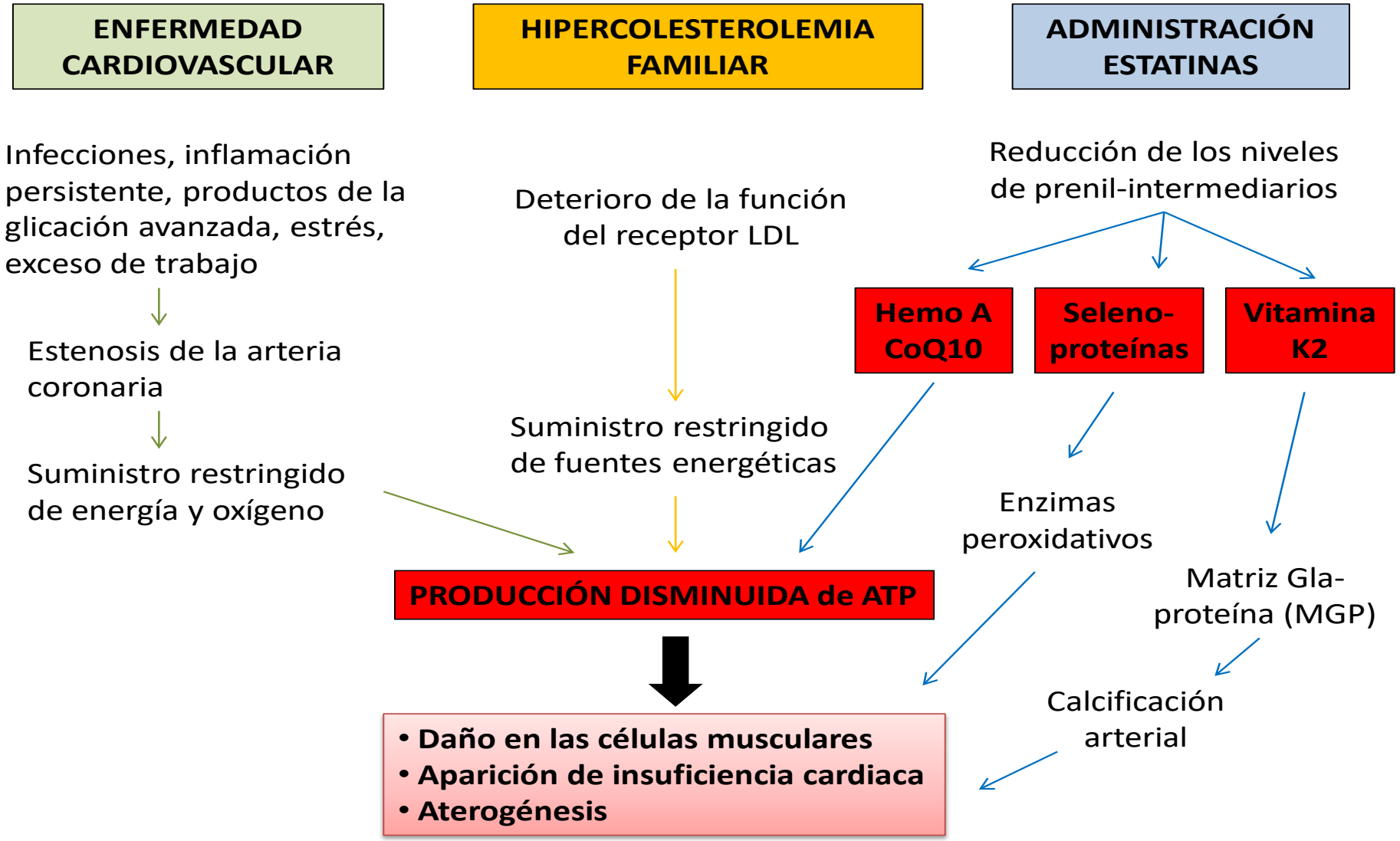
Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms

Expert Rev. Clin. Pharmacol. Early online, 1–11 (2015)

Harumi Okuyama*[1], Peter H Langsjoen[2], Tomohito Hamazaki[3], Yoichi Ogushi[4], Rokuro Hama[5], Tetsuyuki Kobayashi[6] and Hajime Uchino[7]

[1]*Nagoya City University and Institute for Consumer Science and Human Life, Kinjo Gakuin University, 2-1723 Omori, Moriyama, Nagoya 463-8521, Japan*
[2]*Clinical Cardiology Practice, 1107*

In contrast to the current belief that cholesterol reduction with statins decreases atherosclerosis, we present a perspective that statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels through the depletion of coenzyme Q_{10} and 'heme A', and thereby ATP generation. Statins inhibit the synthesis of vitamin K_2, the cofactor for matrix Gla-protein activation, which in turn protects arteries from calcification. Statins inhibit the biosynthesis of selenium containing proteins, one of which is glutathione peroxidase serving to suppress peroxidative stress. An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency. Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs. We propose that current statin treatment guidelines be critically reevaluated.



Okuyama H, Langsjoen PH, Hamazaki T, Ogushi Y, Hama R, Kobayashi T, Uchino H. **Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms.** *Expert Rev Clin Pharmacol.* 2015 Mar;8(2):189-99

ESTATINAS & CoQ10

ESTUDIO	ESTATINAS	DOSIS (mg/día)	DURACIÓN	REDUCCIÓN CoQ10 (%)
Ghirlanda et al, 1993	PRAVASTATINA	20	12 sem	50
Ghirlanda et al, 1993	SIMVASTATINA	20	12 sem	54
Laaksonen et al, 1995	SIMVASTATINA	20	4 sem	32
Davidson et al., 1997	ATORVASTATINA	10-20	1 año	38
Rundek et al. 2004	ATORVASTATINA	80	30 días	52
Ashton et al., 2010	ROSUVASTATINA	40	26 sem	27

↑ dosis → ↑ efecto inhibidor

ESTATINAS & CoQ10

ESTUDIO	ESTATINAS		DURACIÓN	REDUCCIÓN Q10 (%)
Ghirlanda et al, 199?				50
Ghirland				4
				38
Ru			30 días	52
Asht	ATINA	40	26 sem	27

J Am Assoc Nurse Pract. 2014 Feb;26(2):85-90. doi: 10.1002/2327-6924.12046. Epub 2013 Jul 12.

Statins' effect on plasma levels of Coenzyme Q10 and improvement in myopathy with supplementation.

Littlefield N[1], Beckstrand RL, Luthy KE.

Author information

Abstract

PURPOSE: Heart disease is the leading cause of death in the United States. HMG-CoA reductase inhibitors, or statins, are medications at the forefront of the battle against cardiovascular disease. Despite their effectiveness, patient compliance with statins has lagged because of medication cost and adverse effects, namely myopathy. Myopathy is the most common side effect of statin use. The purpose of this review is to report plasma levels of CoQ10 in patients taking statins and then to determine the benefit of Coenzyme Q10 (CoQ10) supplementation on statin-related myopathy as evidenced by symptomatic improvement and increase in serum levels of CoQ10.

DATA SOURCES: CINAHL, Medline, Health Source: Nursing/Academic Edition, and Cochrane Library.

CONCLUSIONS: Evidence from this review suggests that studies showed a significant relationship between statin intake and decreased serum levels of CoQ10. A few studies showed a benefit in symptoms of myalgia or improvement of serum levels of CoQ10 with supplementation. One study showed no benefit of CoQ10 supplementation when taken with statins. There were no risks of supplementation reported in any of the studies.

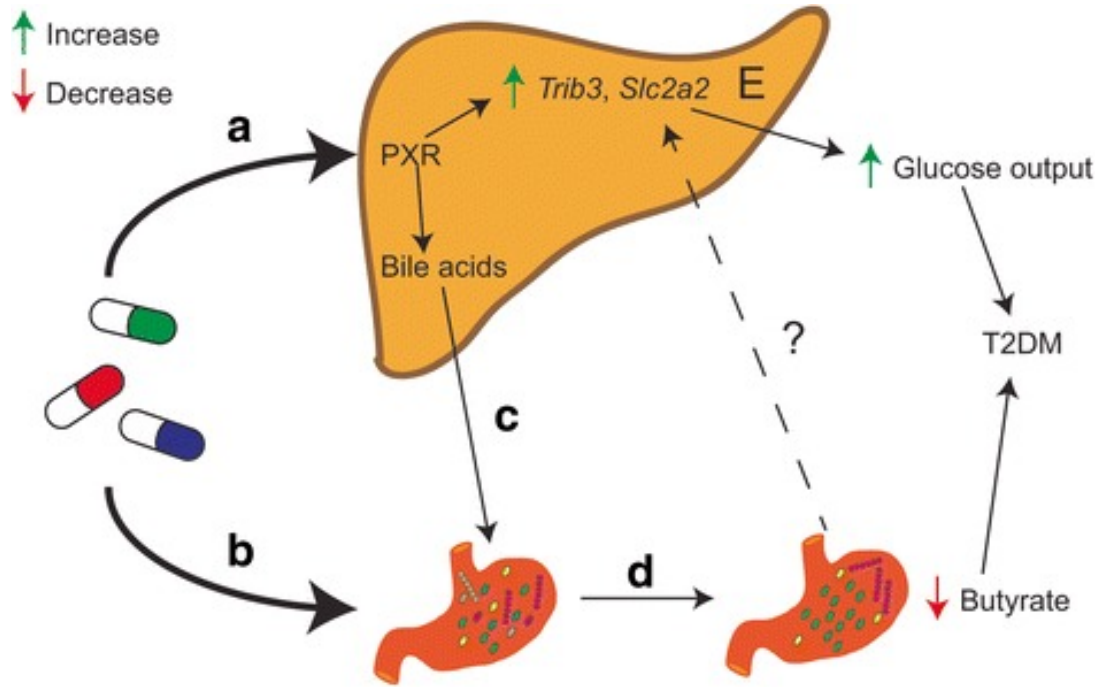
IMPLICATIONS FOR PRACTICE: CoQ10 supplementation might benefit those patients suffering from statin-induced myopathy as evidenced by the results of these studies. Supplementation of CoQ10 at a dose of between 30 and 200 mg daily has shown to have beneficial effects on statin myopathy with no noted side effects. Further research is necessary.

↑ dosis → ↑ efecto inhibidor

ESTATINAS & DISBIOSIS

Mecanismo propuesto por el que las estatinas pueden incrementar el riesgo de DM 2.

Activación PXR en el hígado por las estatinas -> desrregulación de los ác. biliares -> baja diversidad microbiana -> baja producción de butirato



Caparrós-Martín JA, et al.- . **Statin therapy causes gut dysbiosis in mice through a PXR-dependent mechanism.** Microbiome. 2017 Aug 9;5(1):95.

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Article | Published: 06 May 2020

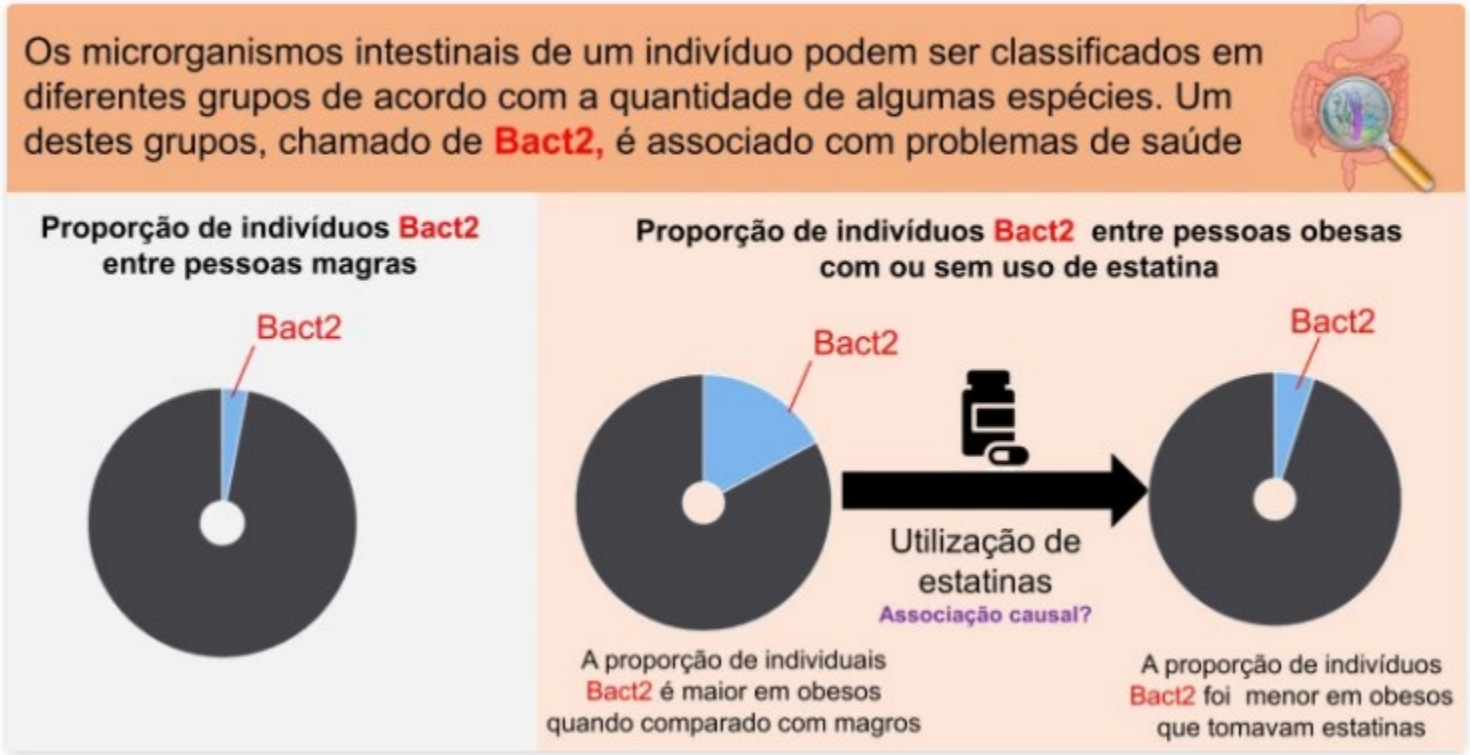
Statin therapy is associated with lower prevalence of gut microbiota dysbiosis

Sara Vieira-Silva, Gwen Falony, [...] Jeroen Raes

Nature **581**, 310–315(2020) | Cite this article

MetaCardis: proyecto UE

888 individuos de Alemania, Francia y Dinamarca



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DOI: 10.4149/BLL_2014_024

Bratisl Lek Listy 2014; 115 (2)

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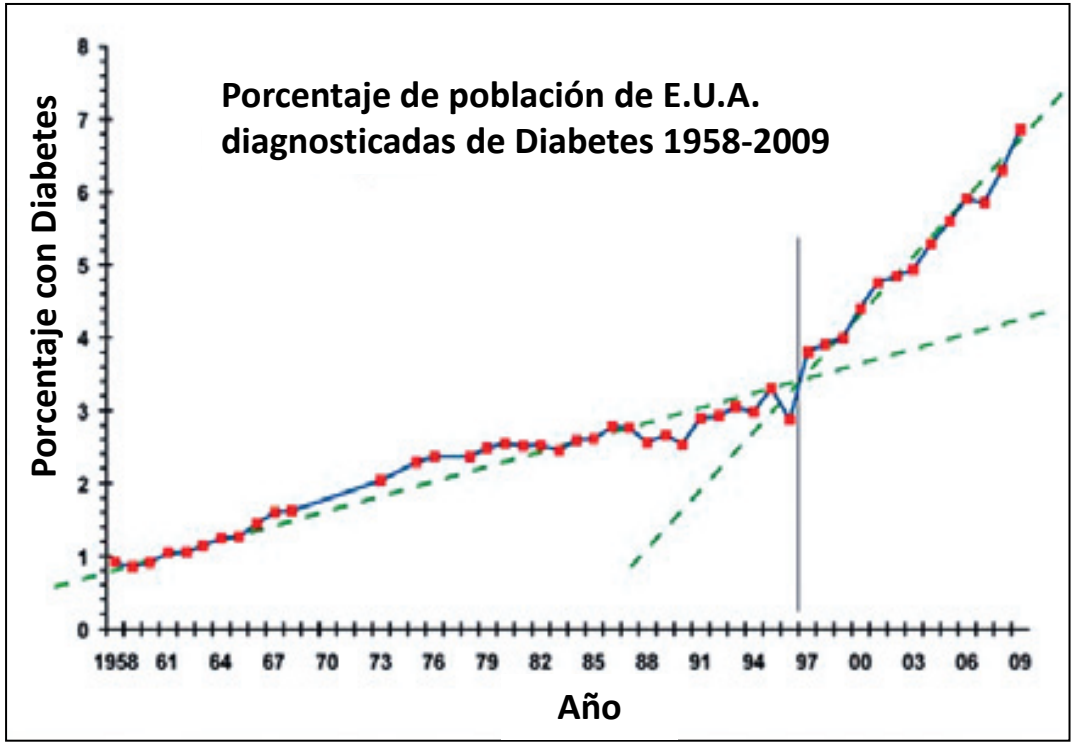
LETTER TO THE EDITOR – COMMENT

Statins, coenzyme Q10 and diabetes type 2

Ginter E

Estudios recientes han demostrado que las estatinas aumentan el riesgo de diabetes tipo II e incluso en un metaanálisis a gran escala mostró su efecto diabetogénico.



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Br J Nutr. 2005 Jan;93(1):131-5.

Acute administration of red yeast rice (Monascus purpureus) depletes tissue coenzyme Q(10) levels in ICR mice.

Yang HT[1], Lin SH, Huang SY, Chou HJ.

7.3.2014 ES Diario Oficial de la Unión Europea L 67/3

REGLAMENTO (UE) Nº 212/2014 DE LA COMISIÓN

de 6 de marzo de 2014

por el que se modifica el Reglamento (CE) nº 1881/2006 en lo que concierne a los contenidos máximos del contaminante citrinina en complementos alimenticios basados en arroz fermentado

	Productos alimenticios (1)	Contenidos máximos (µg/kg)
«2.8	**Citrinina**	
2.8.1	Complementos alimenticios a base de arroz fermentado con levadura roja *Monascus purpureus*	2 000 (*)

(*) El contenido máximo debe revisarse antes del 1 de enero de 2016 a la luz de la información sobre la exposición a la citrinina procedente de otros productos alimenticios y de información actualizada sobre la toxicidad de la citrinina, en particular por lo que respecta a los riesgos de carcinogenicidad y genotoxicidad.».

REGLAMENTO (UE) 2019/1901 DE LA COMISIÓN

de

por el que se modifica el Reglamento
máximos de citrinina en complementos

	«Productos alimenticios (1)	Contenidos máximos (µg/kg)
2.8	**Citrinina**	
2.8.1	Complementos alimenticios a base de arroz fermentado con levadura roja *Monascus purpureus*	100»

2) Se suprime la nota «(*) El contenido máximo debe revisarse antes del 1 de enero de 2016 a la luz de la información sobre la exposición a la citrinina procedente de otros productos alimenticios y de información actualizada sobre la toxicidad de la citrinina, en particular por lo que respecta a los riesgos de carcinogenicidad y genotoxicidad.».

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Gracias ;)