22 ottobre 2023

Nutraceutici: ADME e meccanismi d'azione

Prof. Stefano Dall'Acqua

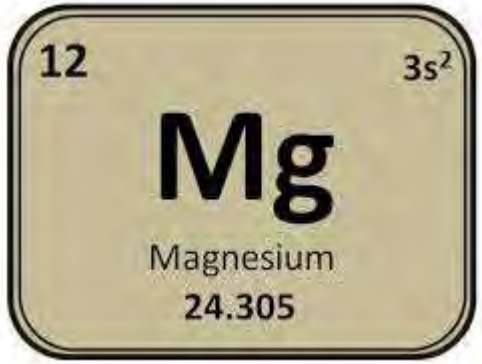
PharmD, PhD, Professore Associato Dipartimento di Scienze del Farmaco, Università degli Studi di Padova

Nutraceutici assorbimento….

Anche composti molto più «semplici» possono avere vie di assorbimento complesse

Pensiamo ai minerali e agli oligoelementi

Quali sono le problematiche e gli aspetti più significativi?



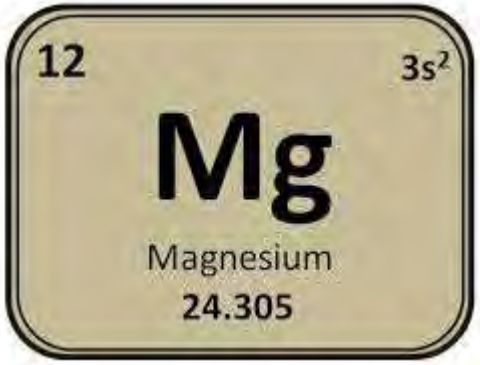
Convolto in più di 300 reazioni metaboliche
Necessario per moltissimi processi biochimici
Un adulto contiene circa 25 g di Mg e circa 50% è nel tessuto osseo
Mg e Ca sono interconnessi (es produzione ATP)
Nell'adulto si consigliano 4,5 mg/Kg/die di assunzione

Stati carenziali si possono osservare nel diabete mellito, sindromi da malassorbimento, ipertiroidismo, alcolismo, anche dopo prolungate terapie con alcuni farmaci
Il deficit di magnesio è causa di ipopotassiemia

Funzioni importanti su muscolo cardiaco
Prevenzione osteoporosi
Crampi
Moltissimi altri usi

ClinBiochemRev. 2003 May; 24(2): 47–66. "Magnesium Metabolism and its Disorders" R Swaminathan

Current Nutrition & Food Science, 2017, *13*, 260-278



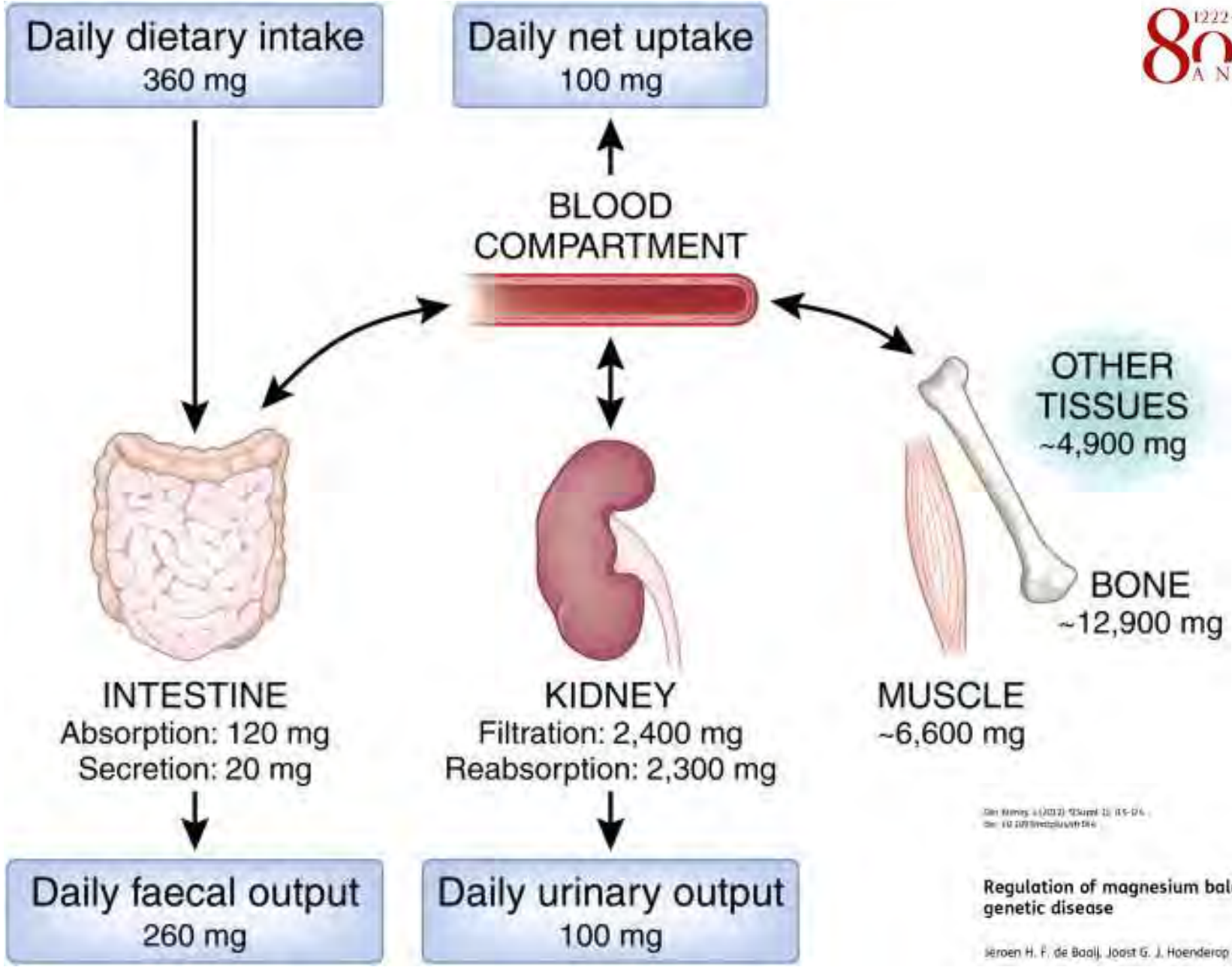
Claims consentiti per Mg

Contribuisce …
-normale funzionamento del SNC
-riduzione stanchezza ed affaticamento
-normale funzione muscolare
-equilibrio elettrolitico
-normale metabolismo energetico
-mantenimento del tessuto di ossa e denti

Fonti
Vegetali a foglia verde (la clorofilla contiene magnesio chelato nella porfirina)
Noci
Cereali non brillati

Ma quali sono le fonti migliori per integrare il magnesio e quali sono le vie per il suo assorbimento?

Qual è il «destino» ed il bilancio con ingresso e uscita di Mg dal nostro organismo?

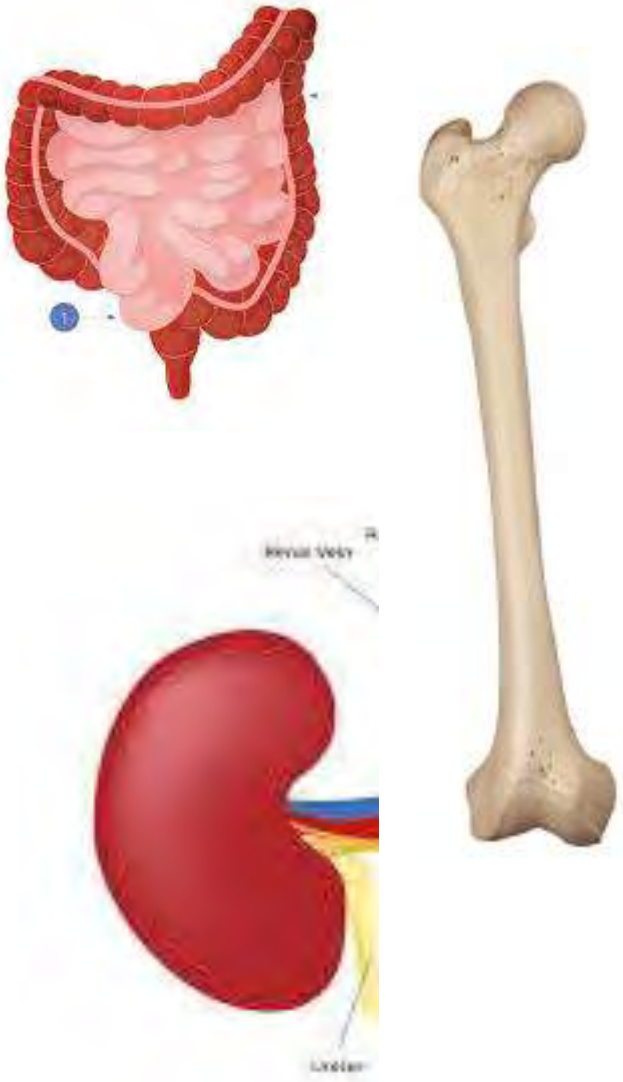


CKJ

Regulation of magnesium balance: lessons learned from human genetic disease

Jeroen H. F. de Baaij, Joost G. J. Hoenderop and René J. M. Bindels

- Mg^{2+} homeostasis depends on three organs: the intestine, facilitating Mg^{2+} uptake; bone, the main Mg^{2+} storage system of the body and the kidneys, which are responsible for Mg^{2+} excretion.
- In the intestine, about 80–90% of Mg^{2+} is absorbed passively through paracellular transport. The remaining Mg^{2+} is absorbed via active Mg^{2+} transporters, which account for the fine-tuning of Mg^{2+} regulation.
- Bone tissue constitutes the largest Mg^{2+} store in the human body, though it is also stored in muscle where it acts to antagonize Ca^{2+} during muscle contraction.
- Mg^{2+} is mainly excreted in the kidney. About 90–95% of daily filtrated Mg^{2+} is reabsorbed in the kidney. Again, the interplay between passive mechanisms and adjustment via active transporters determine the final Mg^{2+} concentration.



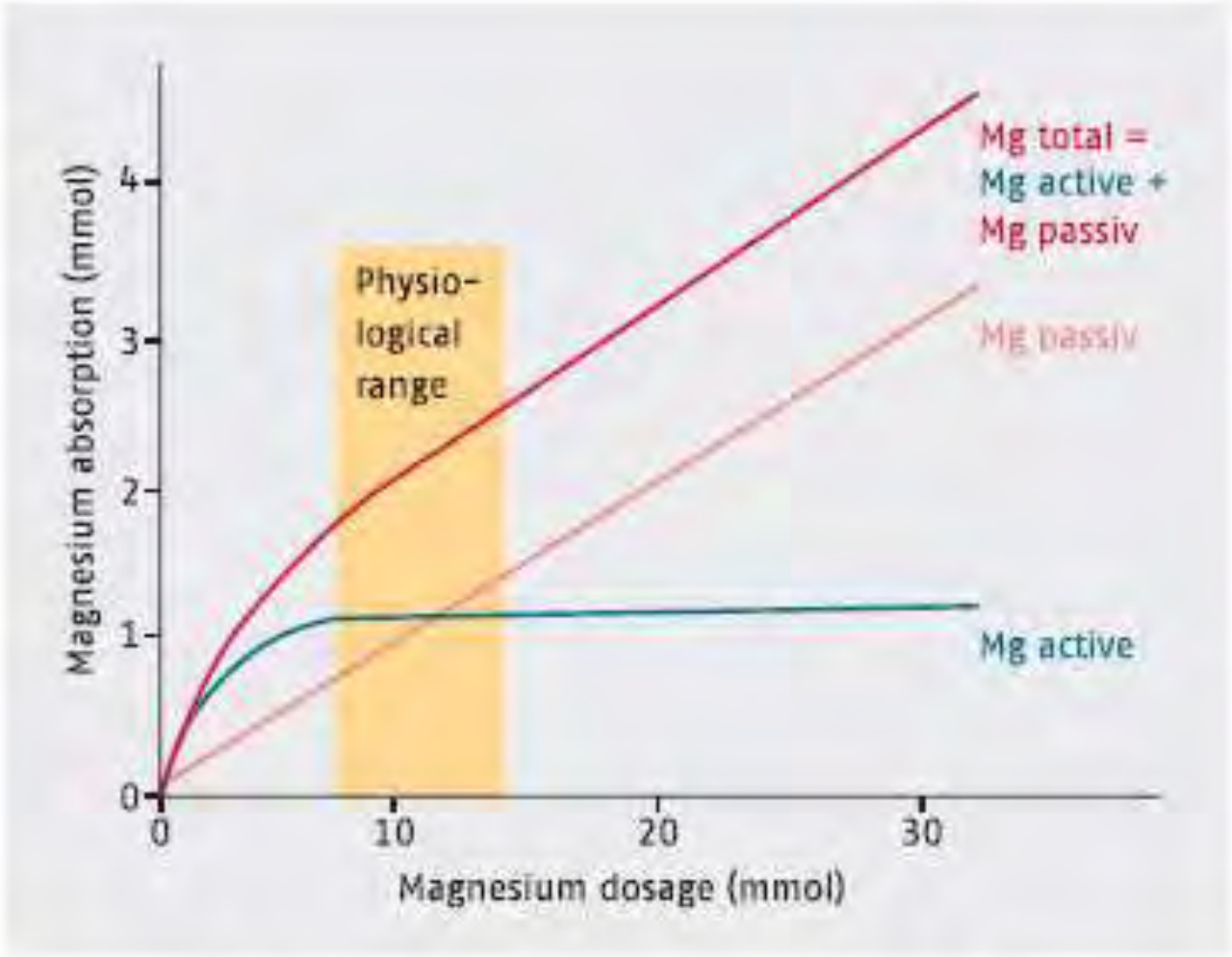


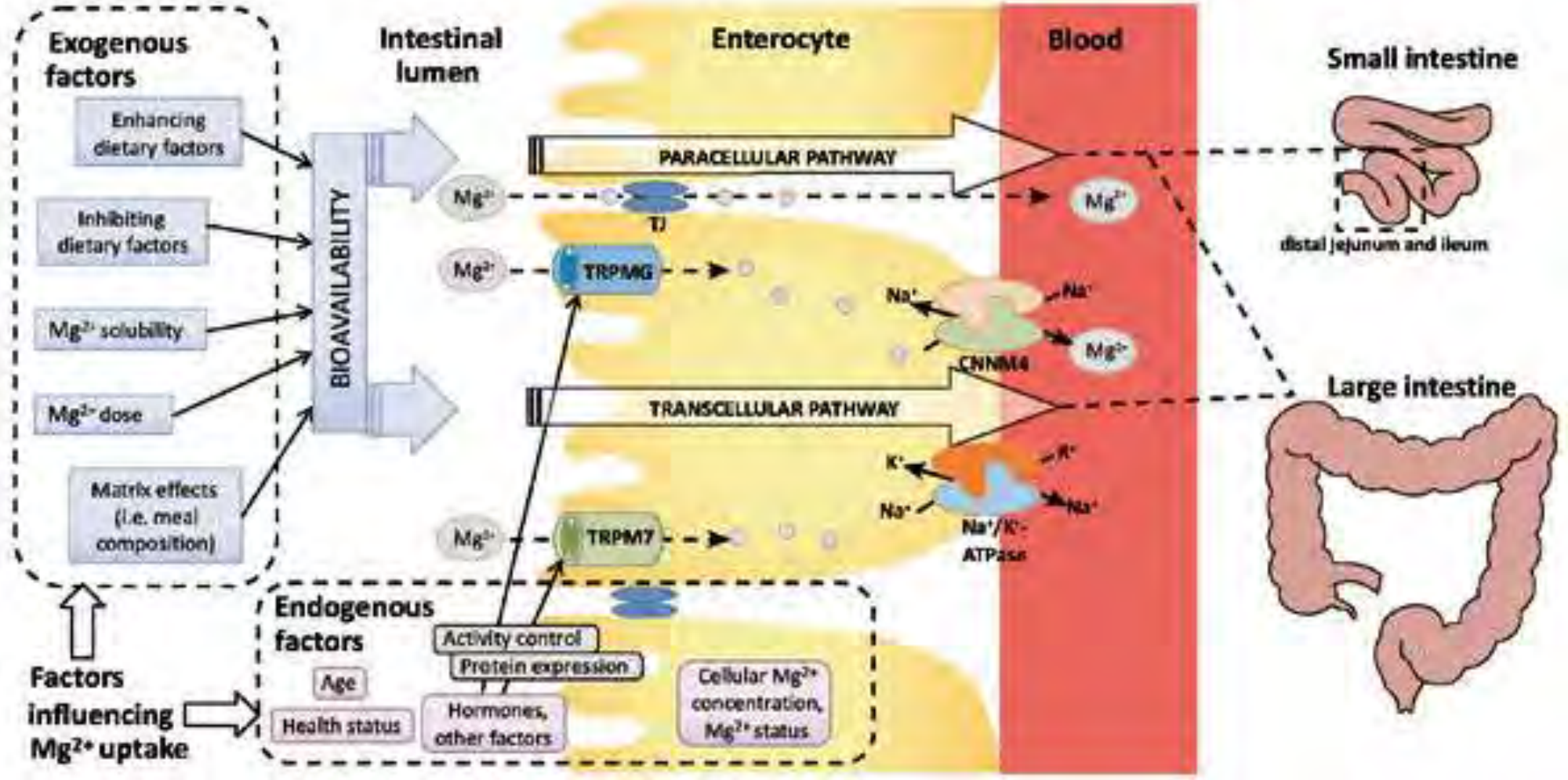
Figure 1. Magnesium absorption.

Table 1: Recommended Dietary Allowances (RDAs) for Magnesium [1]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	30 mg*	30 mg*		
7–12 months	75 mg*	75 mg*		
1–3 years	80 mg	80 mg		
4–8 years	130 mg	130 mg		
9–13 years	240 mg	240 mg		
14–18 years	410 mg	360 mg	400 mg	360 mg
19–30 years	400 mg	310 mg	350 mg	310 mg
31–50 years	420 mg	320 mg	360 mg	320 mg
51+ years	420 mg	320 mg		

*Adequate Intake (AI)

https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#:~:text=In%202022%2C%20FDA%20approved%20a,high%20blood%20pressure%20(hypertension).



Current Nutrition & Food Science, 2017, *13*, 260-278

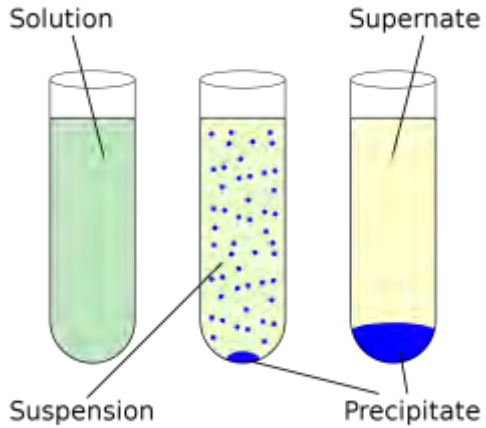
REVIEW ARTICLE

Intestinal Absorption and Factors Influencing Bioavailability of Magnesium-An Update

Fattori Esogeni

Solubilità è importantissima più il sale è solubile più il Magesio sarà assorbito

Forme inorganiche come MgO, MgCl2 sono poco solubili (sale Inglese, sale di Epsom o epsomite sale amaro)



Le forme inorganiche però apportano molto Mg per unità di peso!

Forme organiche sono più solubili, Citrato, pidolato, gluconato etc

Sali organici di magnesio differenti possibilità

Chelati con amminoacidi come glicina o altri
Citrati, picolinati, gluconati, tartrati
Moltissime possibilità
Molto importante la solubilità
Spesso possono essere utilizzate composizioni miste che migliorano alle volte l'aspetto organolettico

Le formulazioni possono essere preparate pensando a tutti questi aspetti combinando differenti fonti di Mg

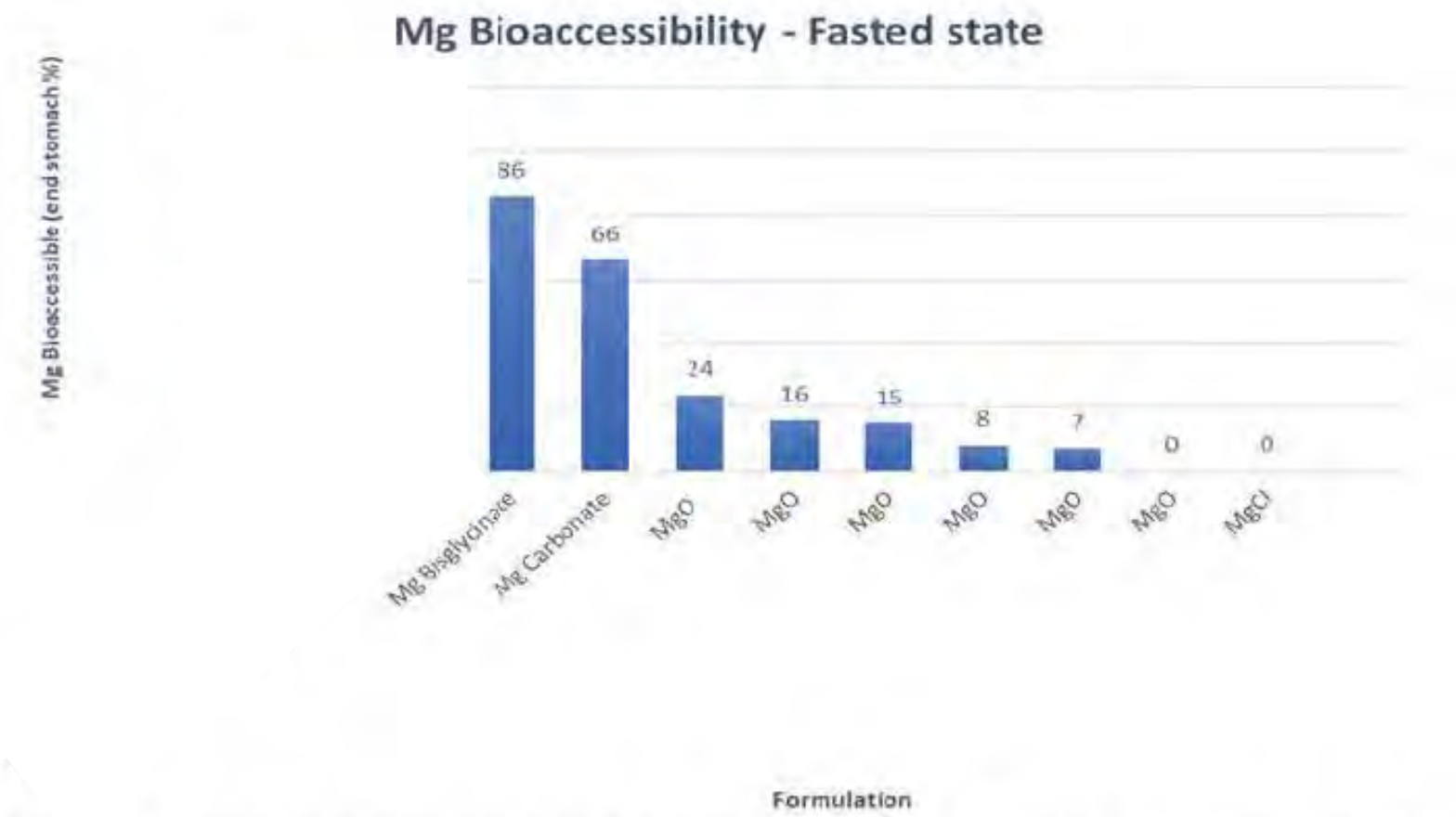


Figure 1: Relative (%) Mg^{2+} release during the stomach incubation upon simulated ingestion of Mg-containing formulations under fasted conditions
Adapted from Blancquaert et al. 2019 [8]

OPEN ACCESS Freely available online
Journal of Nutrition & Food Sciences
Commentary

Type of Magnesium Salt and Formulation Solubility Determines Bioavailability of Magnesium Food Supplements

An-Katrien Vyncke[1*], Geert Vanheule[1], Chris Vervaet[2], Mieke Van Den Driessche[1]

[1]Metagenics Inc., Europe, E. Vlietinckstraat 20, 8400 Oostende, Belgium; [2]Laboratory of Pharmaceutical Technology, Ghent University, 9000 Ghent, Belgium

United States Patent [19]
Ashmead

[11] **Patent Number: 4,599,152**
[45] **Date of Patent: Jul. 8, 1986**

[54] **PURE AMINO ACID CHELATES**

[75] Inventor: **Harvey H. Ashmead**, Kaysville, Utah
[73] Assignee: **Albion Laboratories**, Clearfield, Utah

[21] Appl. No.: **738,065**
[22] Filed: **May 24, 1985**
[51] **Int. Cl.**[4] **C25B 1/02**
[52] **U.S. Cl.** **204/72**; 204/129; 260/113; 260/115
[58] **Field of Search** 204/129, 128, 72; 260/115, 113

[56] **References Cited**
U.S. PATENT DOCUMENTS

3,040,018 6/1962 Wingard 260/115
4,495,176 1/1985 Brule et al. 260/115

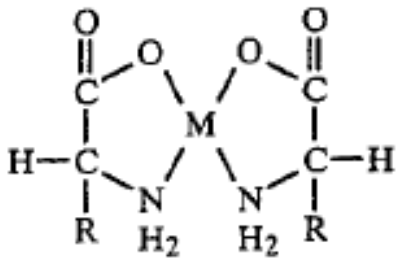
Primary Examiner—R. L. Andrews
Attorney, Agent, or Firm—Thorpe, North and Western

[57] **ABSTRACT**

Pure amino acid chelates and a method of their production are disclosed. The amino acid chelates are free of contaminating inorganic anions. The chelate consists of a metal ion comprising iron, zinc, manganese, magnesium, copper, calcium and mixtures thereof. The metal ion is chelated to one or more ligands comprising alpha amino acids, protein hydrolysates, polypeptides, dipeptides, and combinations thereof. A novel process is disclosed wherein the amino acid ligand is brought into reactive contact with a divalent metal ion in an environment which is completely anion free but otherwise conducive to the interaction between the amino acid ligand and the metal ion, with the formation of an amino acid chelate in pure form or, at least, which can readily be recovered from the reactive environment in pure form.

8 Claims, No Drawings

$$MSO_4 + 2RCHNH_2COOH + 2NaOH \longrightarrow \quad (1)$$

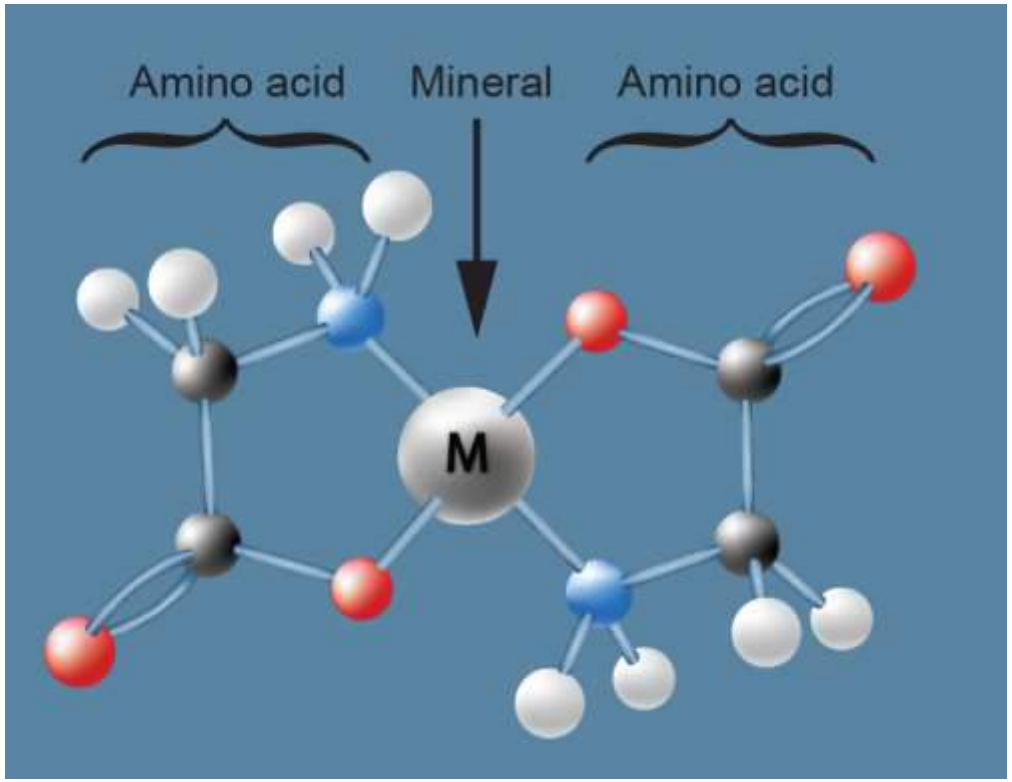


$$+ Na_2SO_4 + 2H_2O$$

where M is a bivalent metal cation and R is a radical of a naturally occurring amino acid.

Preparazione di chelati con amminoacidi e metalli

Si forma un complesso che migliora molte delle caratteristiche del metallo di partenza in termini di solubilità e assorbimento



CHELAZIONE
il metallo viene a formare un complesso con amminoacidi o altra parte organica
Non vi sono legami covalenti col metallo

maggiore solubilità
Maggiore assorbimento

I complessi formati con amminoacidi usano i trasportatori per essere assorbiti!!

Dobbiamo tenere conto della granulometria perchè influenza la solubilità
Quindi anche la micronizzazione può essere un parametro da considerare nelle caratteristiche dell'ingrediente

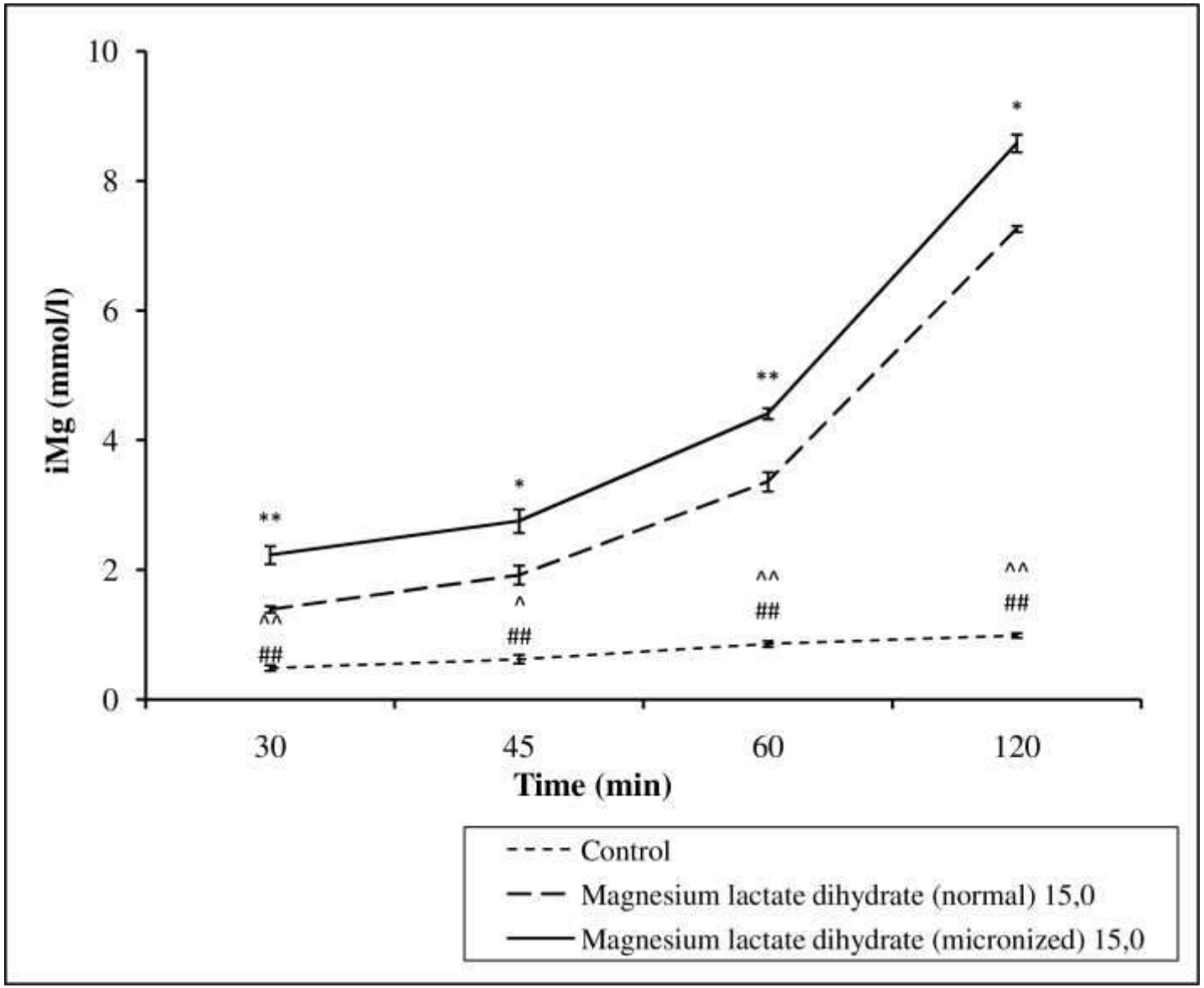


Table 1. Overview of endogenous and exogenous factors affecting absorption of Mg^{2+}.

	Improve Absorption	Impair Absorption
Endogenous Factors	• Low Mg^{2+} status	• Increasing age
		• Balanced Mg^{2+} status • Intestinal dysfunction (*e.g.*, in CD, IBD, or SBS)
Exogenous Factors	• MCT (SFA) (?) • Proteins (?) • Casein phosphopeptides (?) • Low- or indigestible carbohydrates (*i.e.* oligosaccharides, inulin, mannitol and lactulose) • High solubility of Mg^{2+} • Solubilized Mg^{2+} (*e.g.*, effervescent tablets)	• High single Mg^{2+} intake dose • Partly fermentable fibers (hemicellulose) • Non-fermentable fibers (cellulose and lignin) • LCT (?) • Phytate • Oxalate • Pharmacological doses of calcium, phosphorus, iron, copper, manganese and zinc • Slow-release formulations (?)

CD, celiac disease; IBD, inflammatory bowel disease; LCT, long chain triglycerides; MCT, medium chain triglycerides; SBS, short bowel syndrome; SFA, saturated fatty acids.

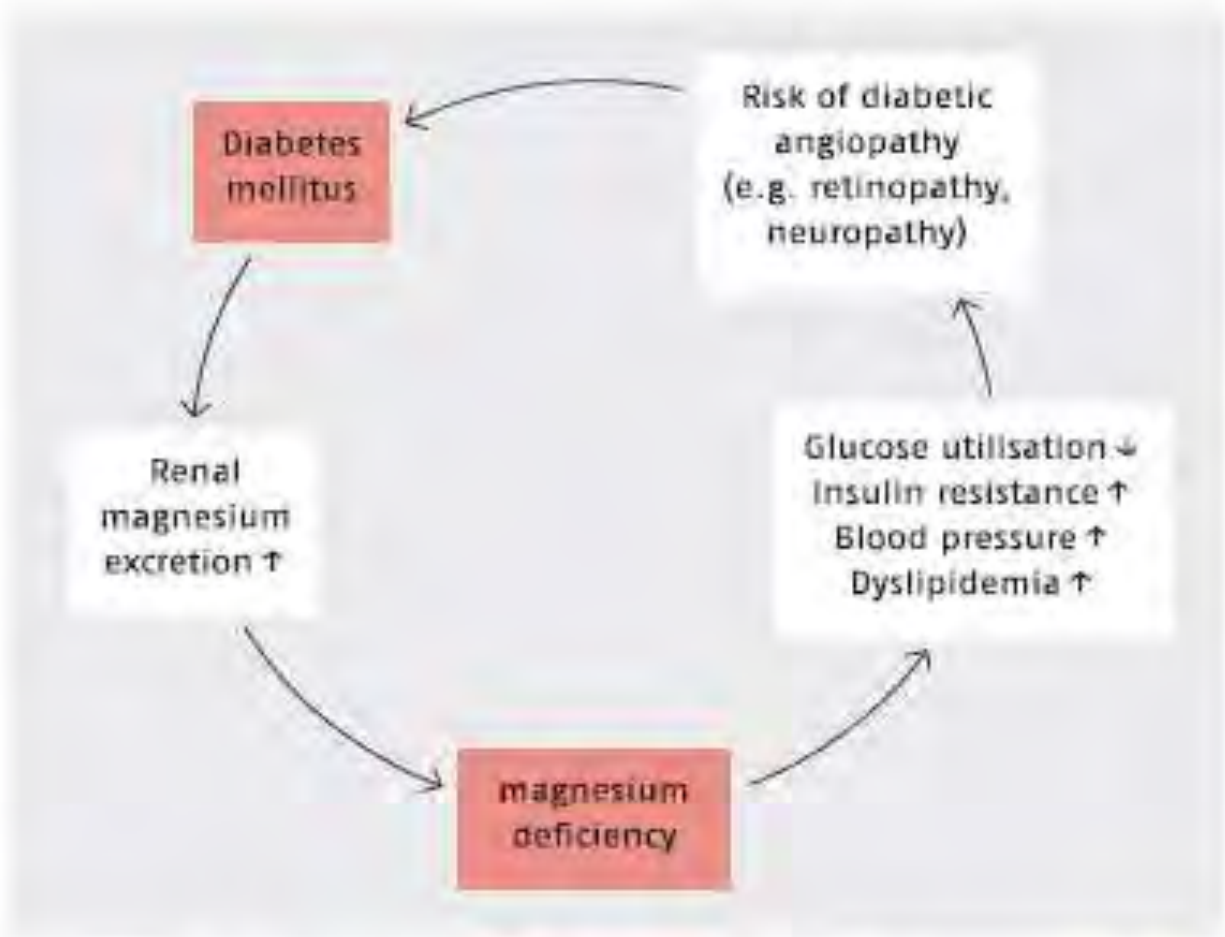


Figure 2. Magnesium deficiency and diabetes [63,71].

Nutrients **2015**, *7*, 8199-8226; doi:10.3390/nu7095388

Review

Magnesium in Prevention and Therapy

Uwe Gröber [1,*], Joachim Schmidt [1] and Klaus Kisters [1,2]

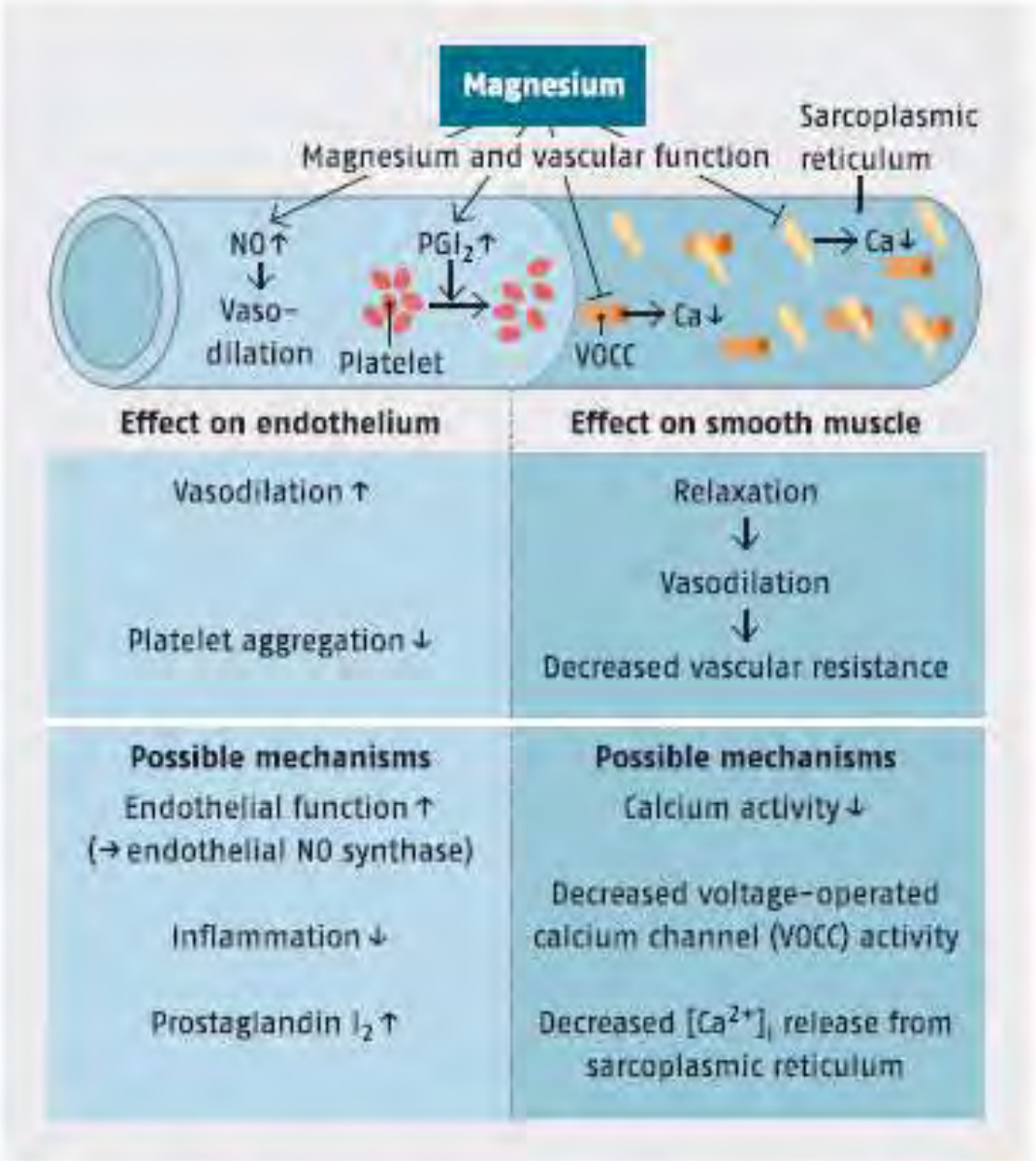


Figure 3. Magnesium and vascular function, according to [52,95].

Nutrients **2015**, *7*, 8199-8226; doi:10.3390/nu7095388

Review

Magnesium in Prevention and Therapy

Uwe Gröber [1,*], Joachim Schmidt [1] and Klaus Kisters [1,2]

Controindicazioni Mg

Soggetti con insufficienza renale o con BAV di grado elevato

Controindicato nella miasteina gravis può peggiorare i sintomi nelle crisi

Sali poco solubili possono dare disturbi gastrointestinali

Soggetti con insufficienza renale possono andare incontro a ipermagnesemia

Interazioni con farmaci Mg

L’assunzione contemporanea con chinolonici, tetracicline può ridurre l’assorbimento del farmaco.

Segnalata riduzione assorbimento con rosuvastatina, atorvastatina, sotalolo, levotiroxina.

Riportato aumento di assorbimento di glibencamide

In generale allontanando le somministrazioni questi effetti sono meno evidenti. Da tenere in considerazione

DIREZIONE GENERALE PER L'IGIENE E LA SICUREZZA DEGLI ALIMENTI E LA NUTRIZIONE

UFFICIO 4

Apporti giornalieri di vitamine e minerali
ammessi negli integratori alimentari
Revisione aprile 2019

MINERALI	UNITA' DI MISURA	APPORTO MASSIMO	DISPOSIZIONI
Calcio	mg	1200	
Fosforo	mg	1200	
Magnesio	mg	450	
Ferro	mg	30	
Zinco	mg	15 per prodotti destinati agli adulti 7,5 per prodotti destinati a bambini (a partire da 3 anni) e adolescenti	Per prodotti eventualmente destinati alla prima infanzia (fino a 3 anni) non può comunque essere superato il VNR di 5 mg (da direttiva 2006/141/CE)
Rame	mg	2	
Manganese	mg	10	
Fluoro	mg	4	Per il fluoro, considerati i fabbisogni dei bambini entro i tre anni di età, è ammesso un apporto minimo pari a 0,25 mg pur se inferiore al 15% del VNR.
Selenio	µg	100	
Cromo	µg	200	
Molibdeno	µg	100	
Iodio	µg	225	
Boro	mg	3,6	Per il boro, per il quale non è previsto un VNR, l'apporto minimo non deve essere inferiore a 0,23 mg.

ZINC

Oregon State University
Linus Pauling Institute

MAIN FUNCTIONS

- Assists in the production of hemoglobin, the oxygen-carrying component of red blood cells
- Critical for normal immune function
- Structural component of hundreds of essential molecules

GOOD SOURCES

Seafood

oysters · crab

- Oysters (steamed), 6 medium, 49.9 mg

Meat

beef · dark meat · pork

- Rib Eye Steak (grilled), 3 ounces, 5.9 mg

Beans

chickpeas · black beans

- Black Beans (canned), ½ cup, 0.7 mg

mg= milligrams; a 3-ounce serving of meat is about the size of a deck of cards

DAILY RECOMMENDATION

Men	Women
11 mg	8 mg

SPECIAL NOTES

- Some dietary factors affect zinc absorption:
  - » Phytates and fiber in whole grains and beans inhibit absorption.
  - » Animal-based protein enhances absorption.
- National dietary surveys indicate that most Americans meet the dietary requirement for zinc.

nutrients

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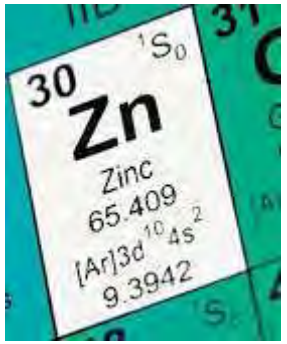
Review

A Guide to Human Zinc Absorption: General Overview and Recent Advances of In Vitro Intestinal Models

Maria Maares [1] and Hajo Haase [1,2,*]



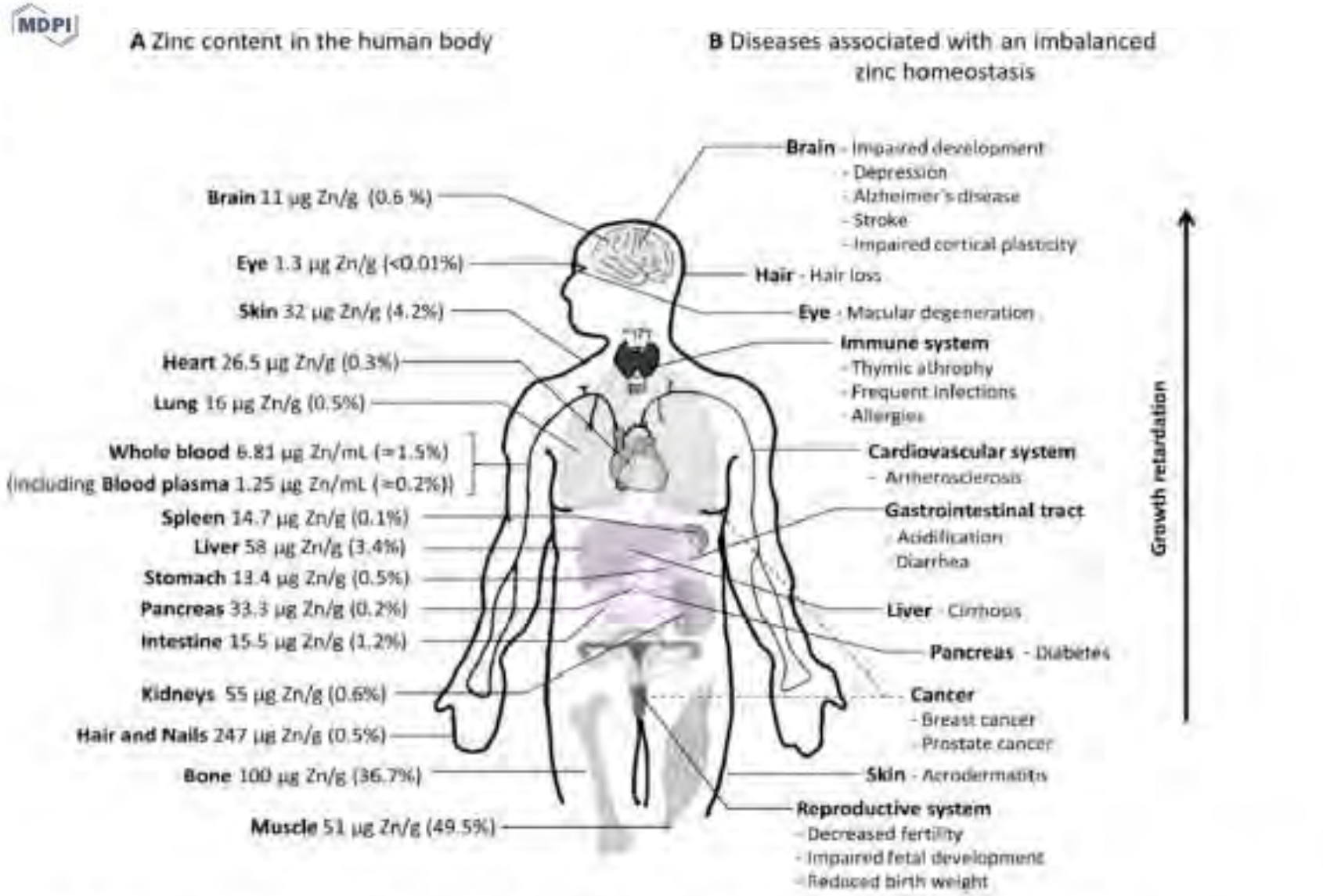
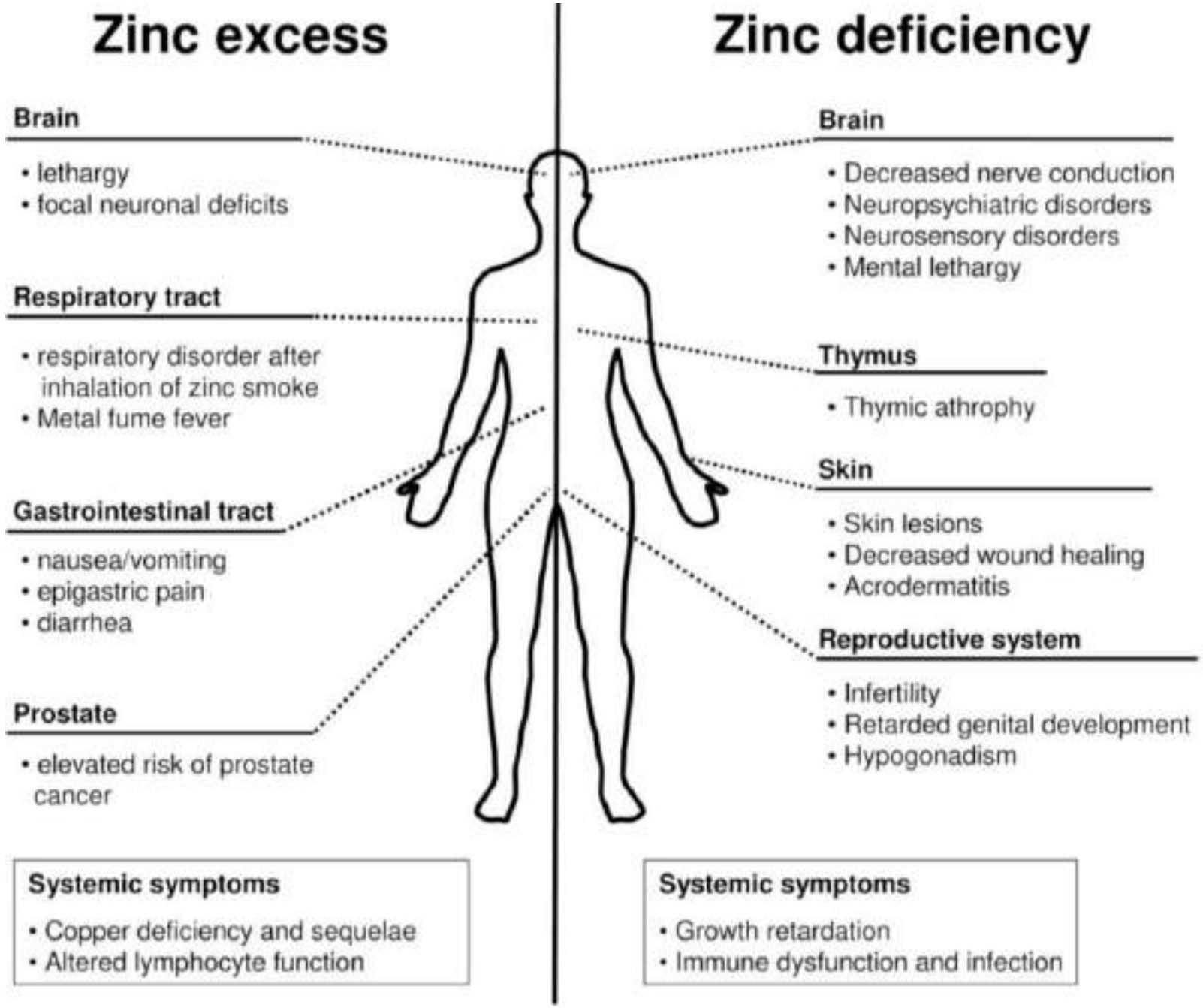
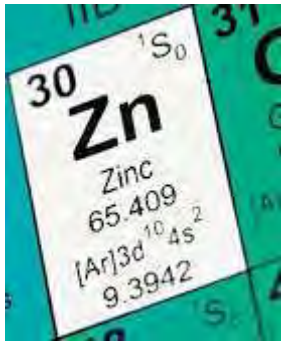


Figure 1. Overview of zinc distribution and disease association in the human body. (**A**) Approximate zinc content (µg per g wet weight) of the respective tissues and the resulting proportion of total body


Zinc excess
Brain
• lethargy
• focal neuronal deficits
Respiratory tract
• respiratory disorder after inhalation of zinc smoke
• Metal fume fever
Gastrointestinal tract
• nausea/vomiting
• epigastric pain
• diarrhea
Prostate
• elevated risk of prostate cancer
Systemic symptoms
• Copper deficiency and sequelae
• Altered lymphocyte function
Zinc deficiency
Brain
• Decreased nerve conduction
• Neuropsychiatric disorders
• Neurosensory disorders
• Mental lethargy
Thymus
• Thymic athrophy
Skin
• Skin lesions
• Decreased wound healing
• Acrodermatitis
Reproductive system
• Infertility
• Retarded genital development
• Hypogonadism
Systemic symptoms
• Growth retardation
• Immune dysfunction and infection

Claim dello zinco

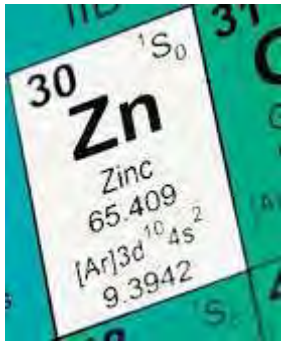


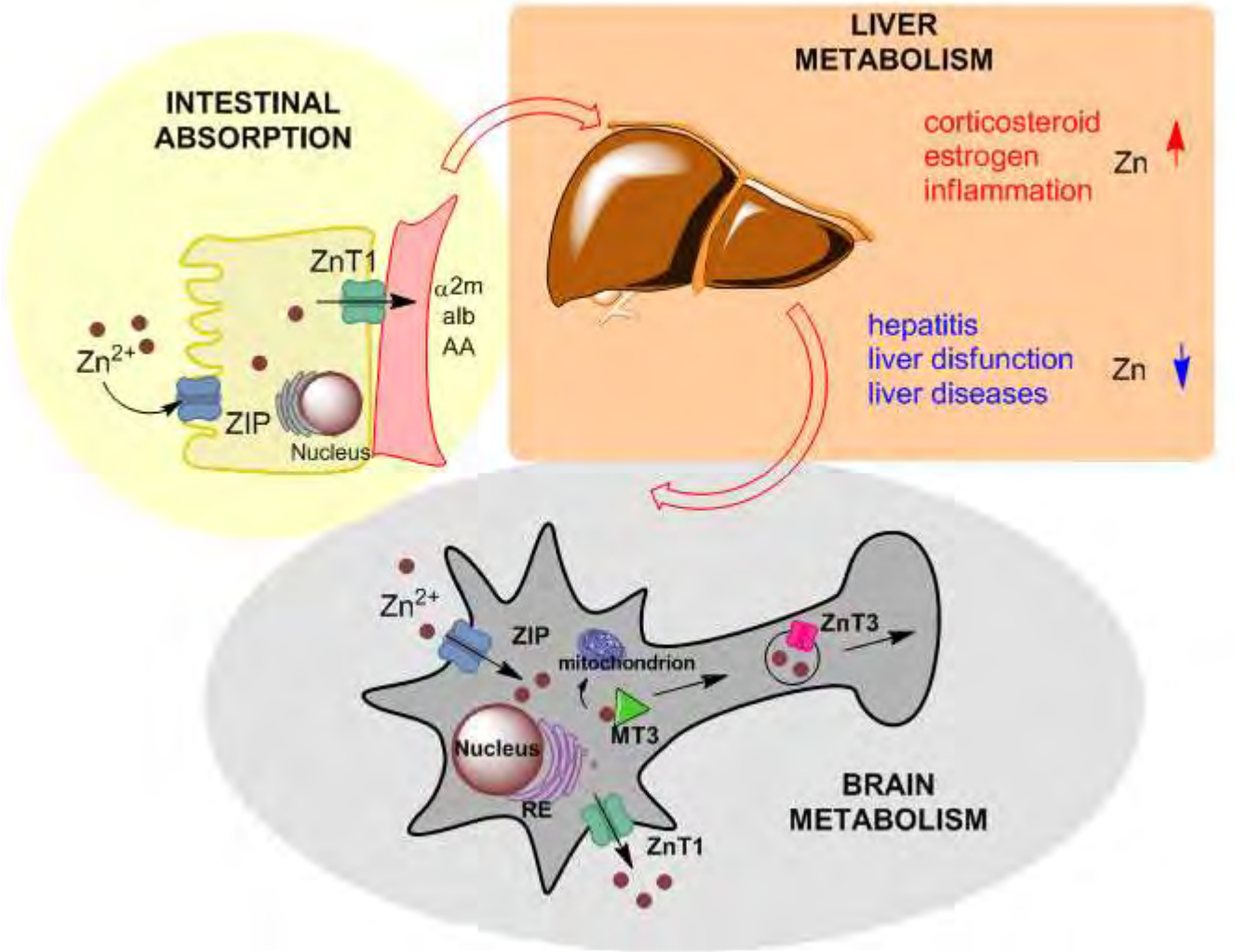
Contribuisce alla funzione del sistema immunitario

Protezione delle cellule dallo stress ossidativo

Contribuisce alla funzione del sistema immunitario

Protezione delle cellule dallo stress ossidativo





biomolecules

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Review

Zinc Therapy in Early Alzheimer's Disease: Safety and Potential Therapeutic Efficacy

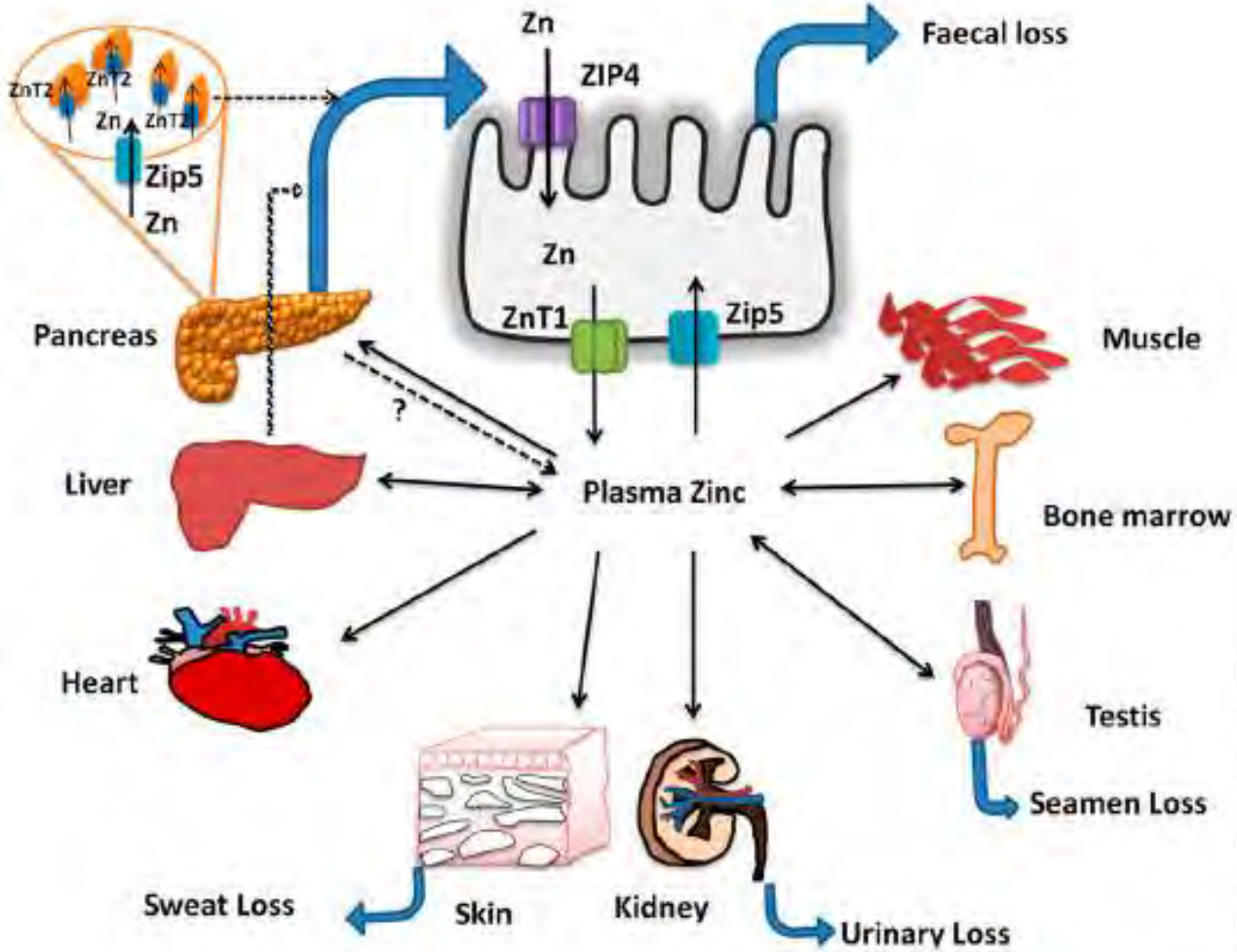


Figure 2. Zinc absorption and homeostasis: Dietary zinc and zinc excreted through pancreatic secretions are absorbed via ZIP4 at the apical surface of the enterocyte and are transported into circulation via ZnT1. The zinc in the plasma bound to albumin (major portion) or in free form is taken up by the peripheral tissues such as liver, bone marrow, testis, kidney, skin, heart, skeletal muscle, and pancreas. In the pancreas, ZIP5 sequesters the zinc from plasma, and it is incorporated in to zymogen granules via ZnT2 and excreted via pancreatic secretions. The absorbed zinc is lost through feces, urine, semen and sweat, among which fecal excretion is sensitive to zinc status of the host. In addition, during zinc insufficiency, the plasma zinc levels are maintained via secretion of zinc only from specific tissues such as liver, bone marrow, and testes while it is strictly conserved in heart, skeletal muscle, skin, and kidney. Thus, enteric excretion of zinc via biliary-pancreatic axis maintains the zinc balance via modulation of excretion during repletion, while zinc depletion is countered via increased ZIP4 mediated absorption in the intestine. Further, during deficiency, few specific tissues release the zinc into the plasma (double arrows) and contribute to the maintenance of plasma zinc pool during inadequate intakes or deficiency.

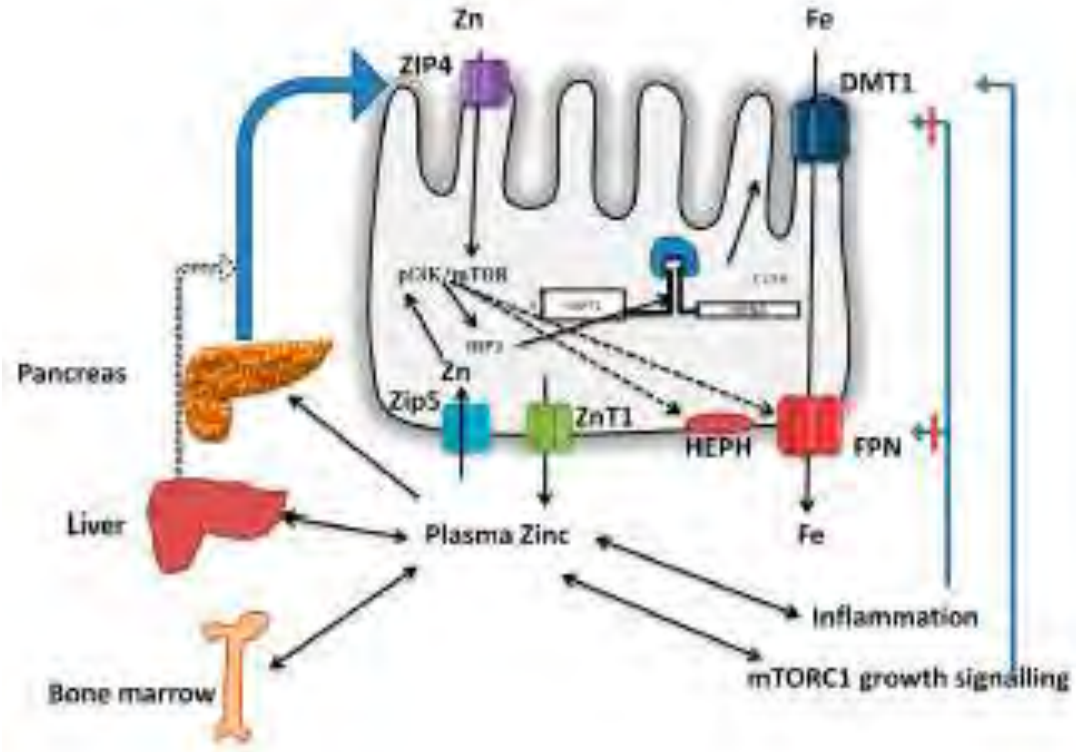


Figure 3. Hypothetical model for direct and indirect effects of zinc on intestinal iron absorption and iron homeostasis: During adequate zinc status and dietary intakes, the biliary-pancreatic zinc secreted into the intestinal lumen stimulates the intestinal iron transport via PI3K-IRP2-DMT1 and FPN1. During inadequate zinc intake, reduced pancreatic zinc levels reduces intestinal iron transporter DMT1 and FPN1 expression, leading to increased retention and inhibition of absorption. Similarly, excretion of zinc from tissues such as liver and bone marrow results in declined tissue zinc, and as a consequence reduced FPN1 expression, leading to reduced secretion for erythropoietic needs. Alternately, zinc might prevent inflammation and thus negate its inhibitory effect on iron absorption. During zinc sufficiency, growth signaling mediated by mTORC1 pathway might increase the iron requirements and thus improve iron absorption.

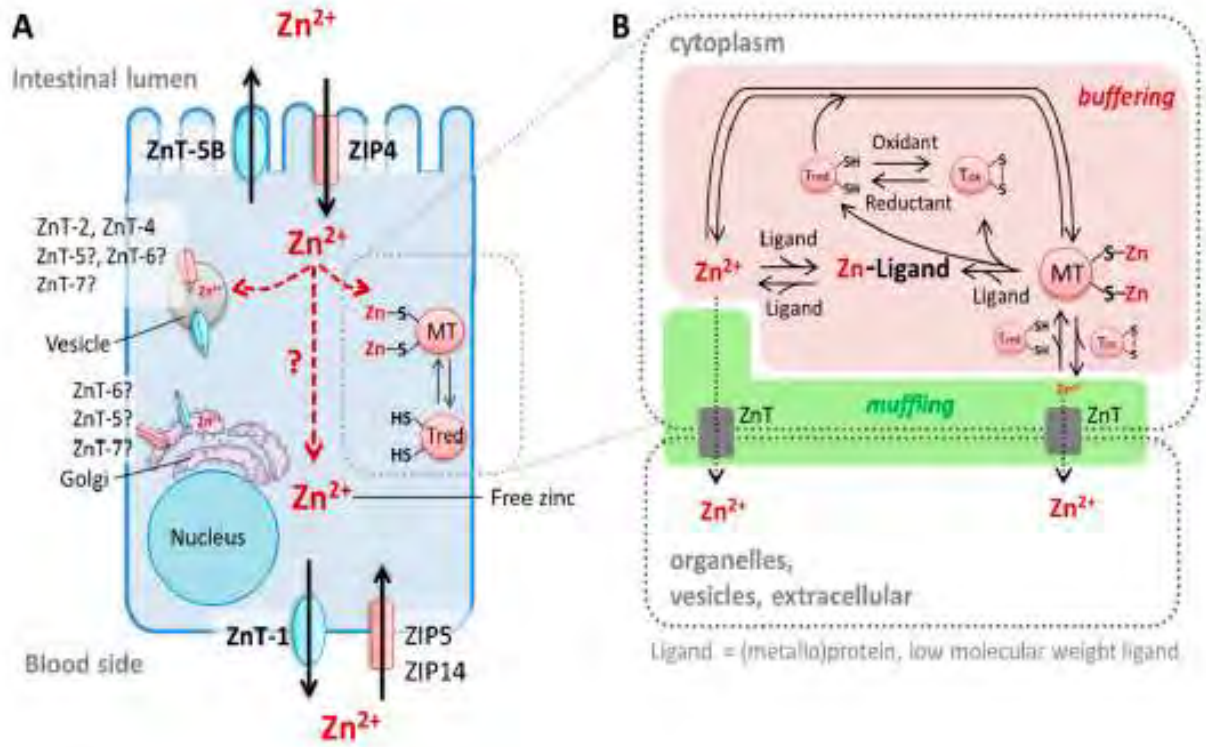


Figure 2. Enterocyte zinc homeostasis. (**A**) Zinc homeostasis in enterocytes during zinc absorption. Three main zinc pools in enterocytes have been described: (i) cytoplasmic-free zinc, which is only complexed by low molecular weight ligands, (ii) protein-bound zinc, depicted here as metallothionein (MT)-bound zinc, and (iii) free zinc stored in vesicles [104]. The vesicular [102,103] and cytoplasmic-free zinc pools [101] are recognized to be involved in zinc absorption by enterocytes [105]. Cellular zinc homeostasis is maintained by three main groups of proteins: the zinc transporter (ZnT)-and the Zrt-, Irt-like protein (ZIP)-family as well as the zinc-binding metallothioneins [99]. They regulate the cytoplasmic-free zinc concentration and provide its distribution into organelles and vesicles. Exporters of zinc from vesicular stores in enterocytes remain to be identified and transfer of the divalent cation through the enterocytes after its uptake by the cells (illustrated by red arrows) is not yet fully understood. (**B**) Zinc buffering and muffling role of metallothioneins (MTs). MTs and other ligands (such as proteins) bind free zinc and, thereby, buffer its cytoplasmic concentration. In addition to zinc transporters, MTs represent zinc muffling moieties, which decrease free zinc content in the cytoplasm by transferring the cation to transporters, sequestering it into organelles, vesicles, or outside the cell. Notably, free zinc itself can also be transported into organelles, whereby, in this process, the ZnT solely undertakes the muffling [100]. Moreover, MTs re-distribute intracellular zinc by transferring it to other ligands, such as metalloproteins [106]. This zinc transfer may be enforced by a redox-active mechanism in which the apo-protein Thionein (Tred) binds the cation, which results in its metal-loaded form, MT, which releases zinc upon its oxidation to Thionin (Tox) (reviewed in Reference [107]).

nutrients

MDPI

Review

A Guide to Human Zinc Absorption: General Overview and Recent Advances of In Vitro Intestinal Models

Maria Maares [1] and Hajo Haase [2,*]

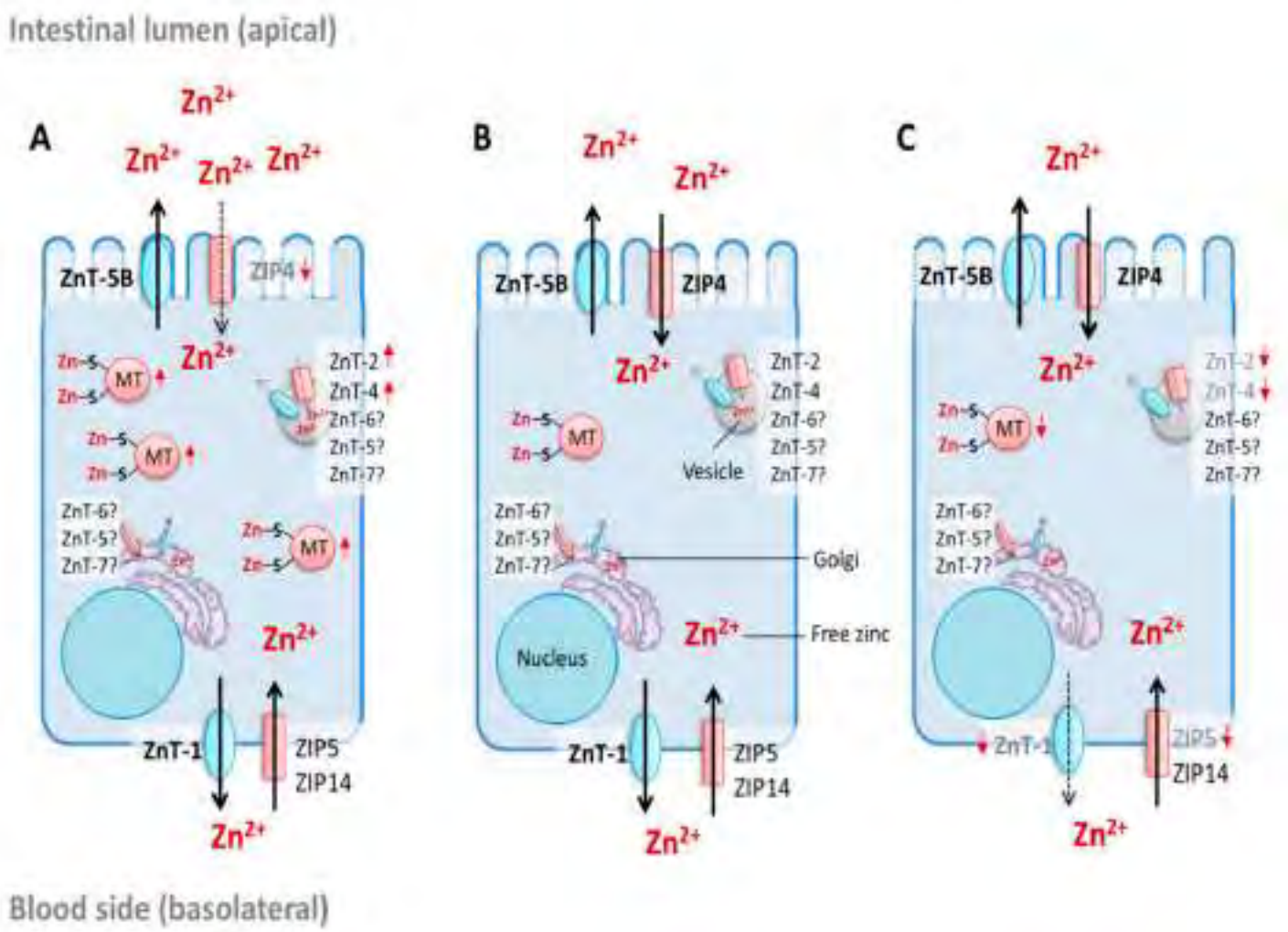


Figure 3. Regulation of intestinal zinc absorption. Potential regulatory mechanisms of zinc absorption into enterocytes during (**A**) zinc excess, (**B**) adequate supply, and (**C**) zinc deficiency, based on experimental data on the zinc-dependent expression pattern of the intestinal zinc transporters (ZnT) and the Zrt-, Irt-like protein (ZIP)-transporters as well as metallothioneins (MT). Enterocyte zinc homeostasis is controlled by these proteins, regulating the amount of intestinally absorbed and basolaterally exported zinc [150]. The subcellular localization of ZnT-5, ZnT-6, and ZnT-7 in enterocytes is not yet fully investigated. Zinc-dependent up-regulation or downregulation of the respective protein and/or messenger ribonucleic acid (mRNA) are indicated by red arrows.

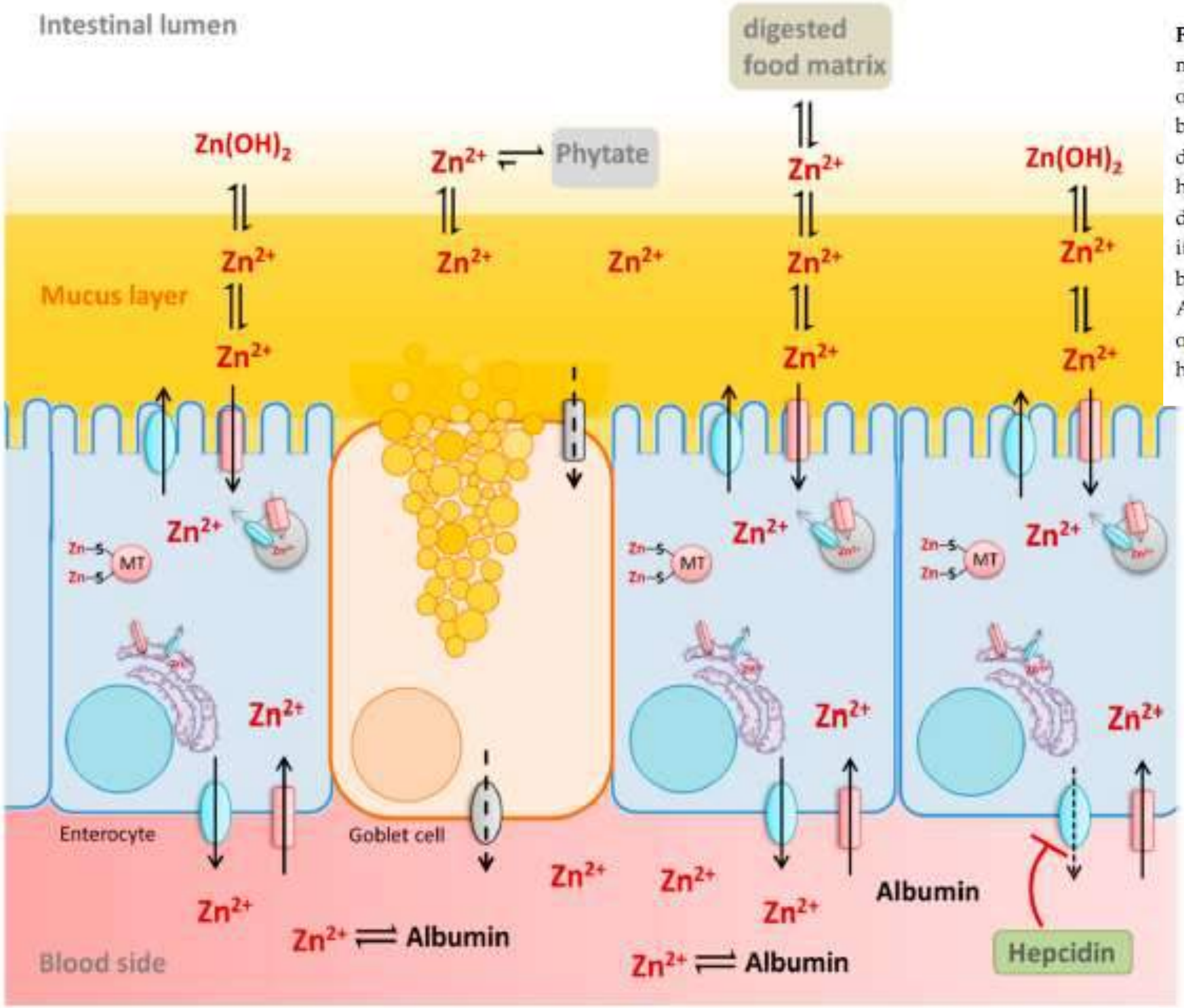
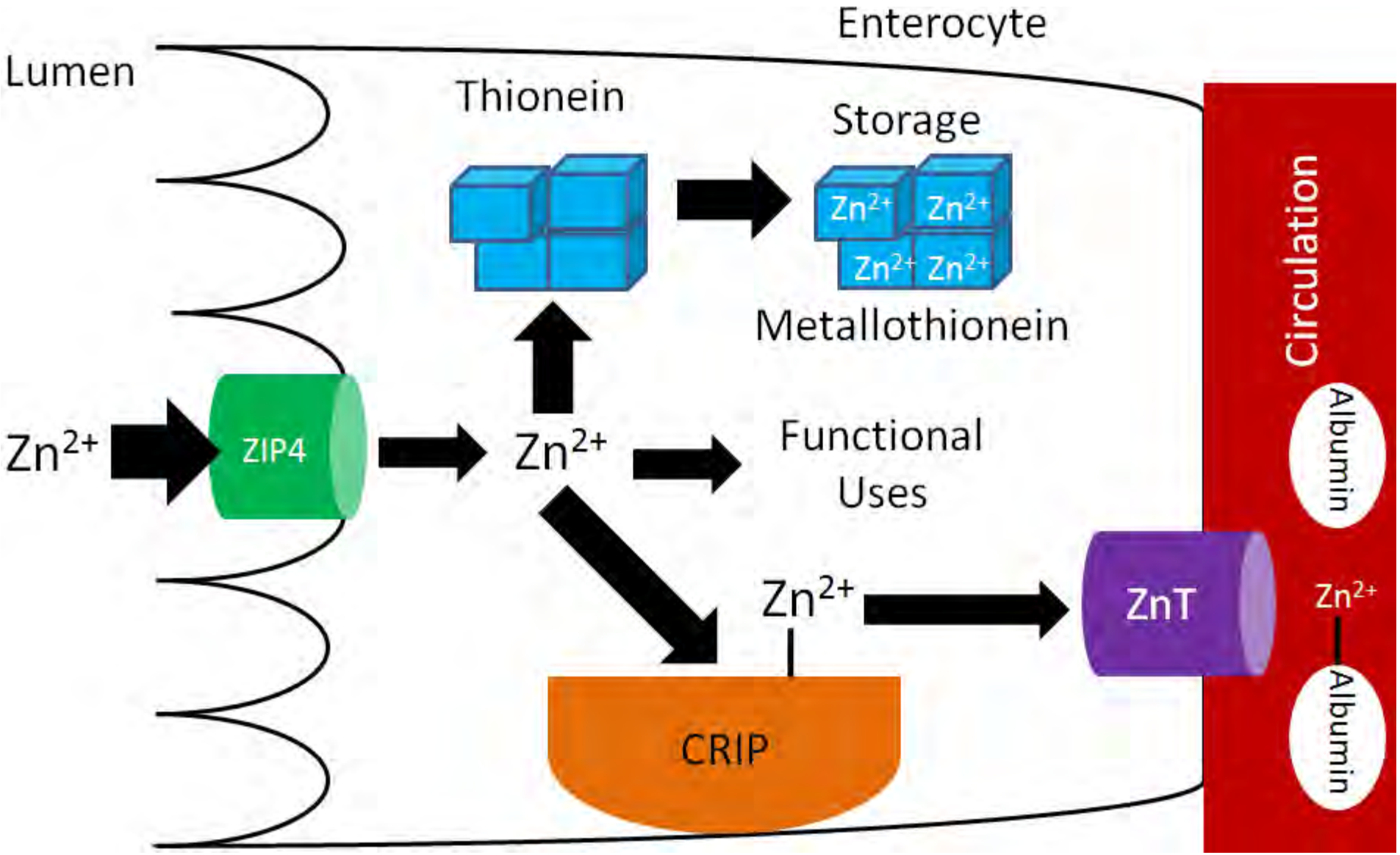
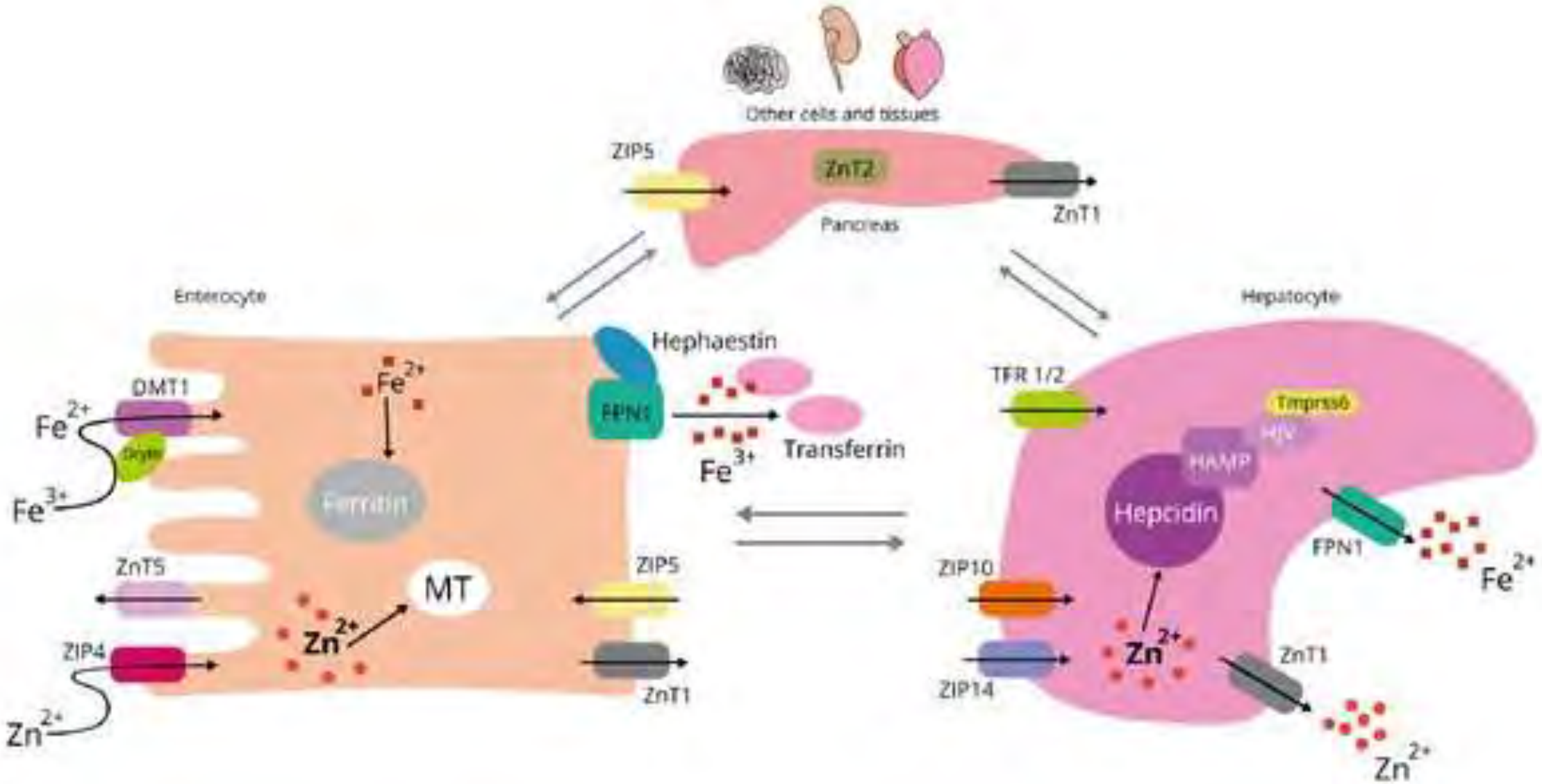
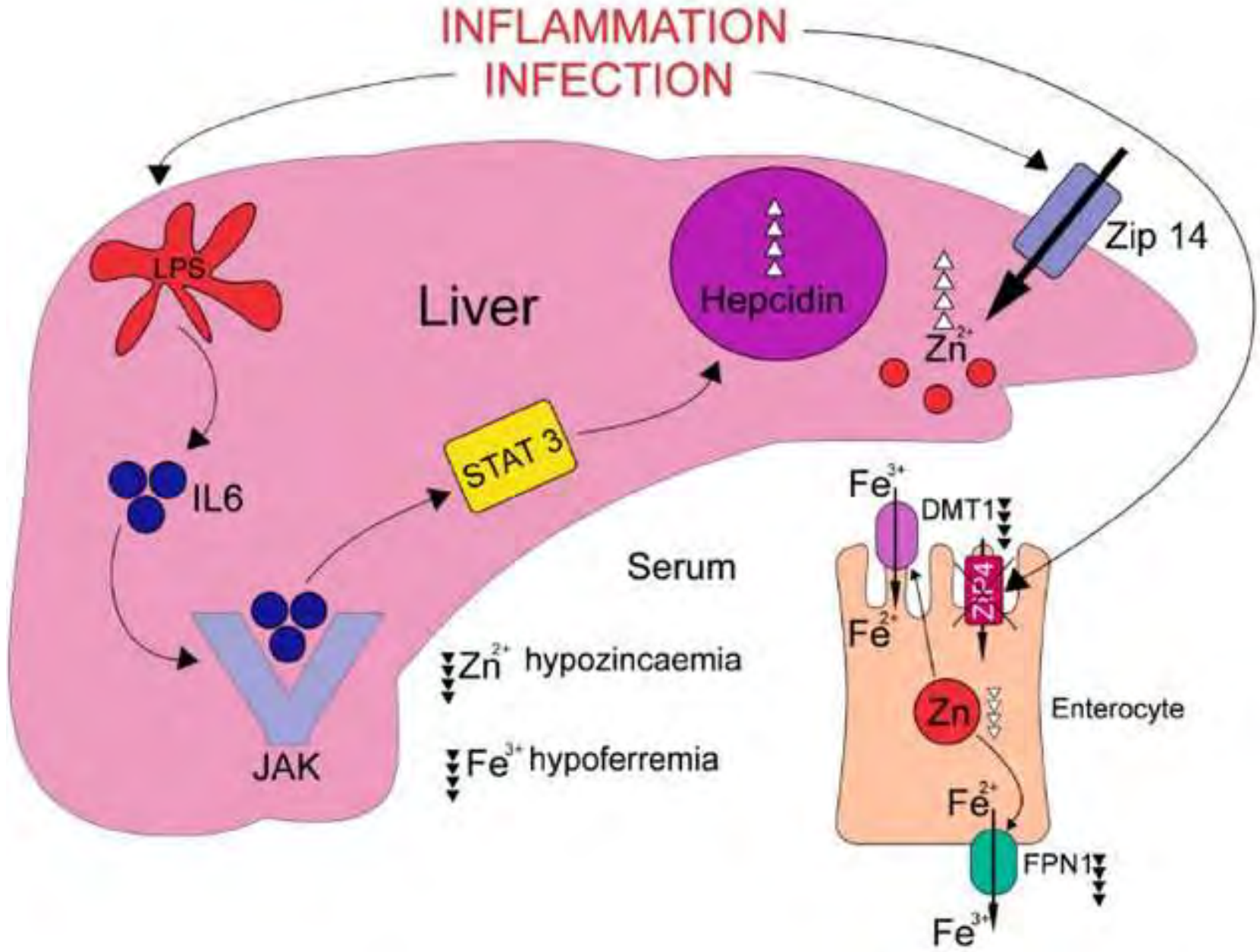


Figure 4. Luminal and serosal factors recognized to influence zinc absorption. Food-derived macromolecules and low molecular weight ligands positively or negatively influence the speciation of the ion as well as its luminal free and available concentration, consequently affecting its absorption by the intestinal epithelium [3]. Phytate forms stable complexes with zinc at intestinal pH, which diminishes its availability for enterocytes [153]. Conversely, the protein content of the consumed food has a positive effect on zinc absorption due to the release of amino acids and peptides upon degradation. Presumably, these increase luminal solubility of the metal, and, consequently, enhance its availability to enterocytes [154,155]. Serum albumin is an important serosal factor, acting as a basolateral zinc-acceptor and enhancing enterocytic zinc release into the blood circulation [102]. Additionally, systemic humoral factors, such as hepcidin, seem to influence ZnT-1-mediated export of zinc by intestinal cells [156], which indicates that the liver might play an important role in secreting humoral factors regulating intestinal zinc absorption.



cysteine-rich intestinal protein (CRIP)


Other cells and tissues
ZIP5
ZnT2
ZnT1
Pancreas
Enterocyte
Hepatocyte
Hephaestin
DMT1
Fe^{2+}
Dcytb
Fe^{3+}
Fe^{2+}
FPN1
Fe^{3+}
Transferrin
Ferritin
TFR 1/2
Tmprss6
HJV
HAMP
Hepcidin
FPN1
Fe^{2+}
ZnT5
MT
ZIP5
ZIP10
ZIP4
Zn^{2+}
Zn^{2+}
ZnT1
ZIP14
ZnT1
Zn^{2+}


INFLAMMATION
INFECTION
LPS
Liver
Hepcidin
Zip 14
Zn2+
IL6
STAT 3
JAK
Serum
Zn2+ hypozincaemia
Fe3+ hypoferremia
Fe3+
DMT1
ZIP4
Fe2+
Zn
Enterocyte
Fe2+
FPN1
Fe3+

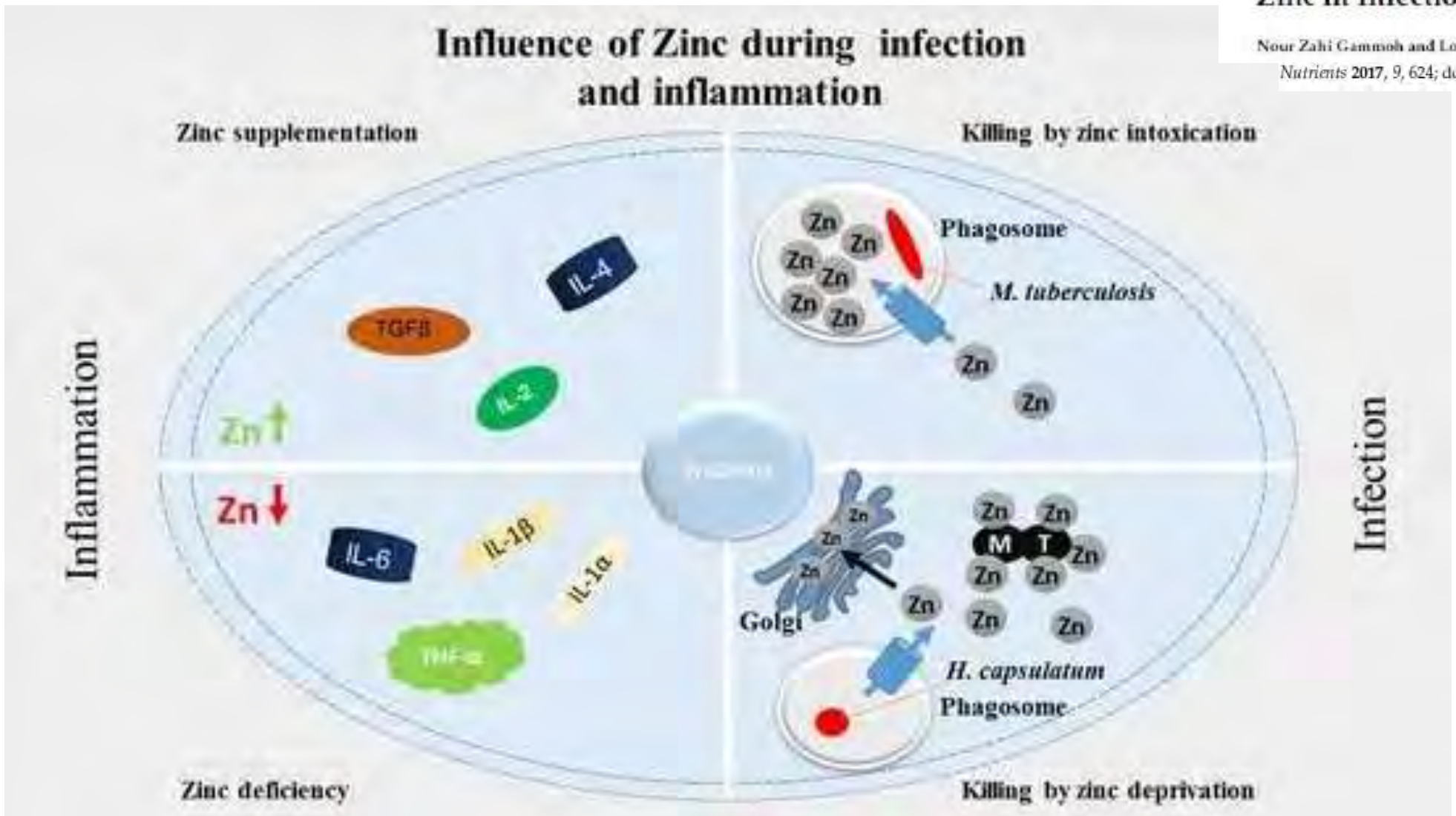
nutrients

Review

Zinc in Infection and Inflammation

Nour Zahi Gammoh and Lothar Rink *

Nutrients **2017**, *9*, 624; doi:10.3390/nu9060624



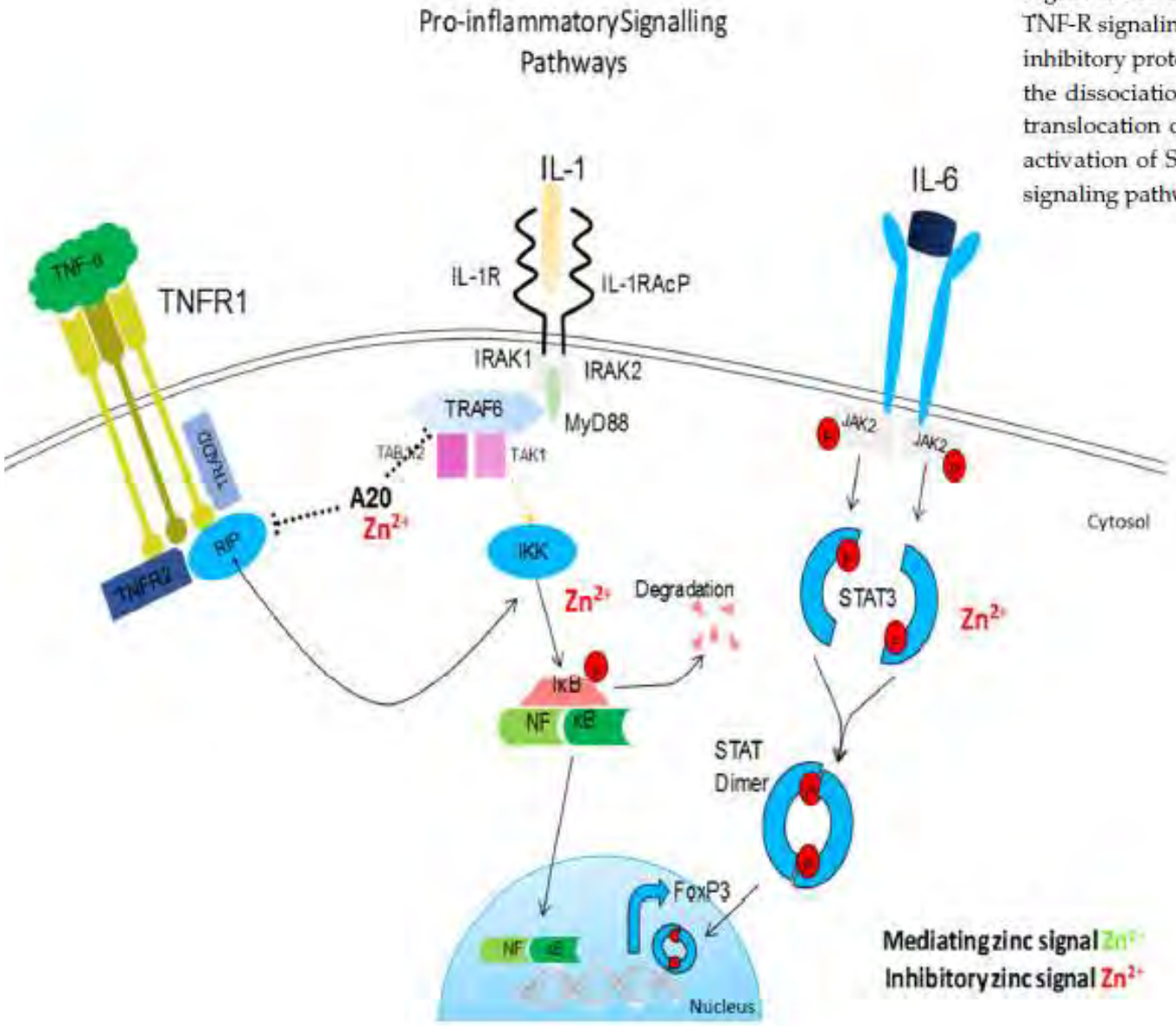


Figure 2. Pro-inflammatory signaling pathway influences by zinc. Similar to TLR signaling, IL-1, and TNF-R signaling pathways converge on a common IκB kinase complex that phosphorylates the NF-κB inhibitory protein, resulting in the release of NF-κB and its translocation to the nucleus. Zinc prevents the dissociation of NF-κB from its corresponding inhibitory protein, thus preventing the nuclear translocation of NF-κB and inhibiting subsequent inflammation. Zinc also inhibits IL-6-mediated activation of STAT3. Zinc acts as anti-inflammatory element influencing major pro-inflammatory signaling pathways.

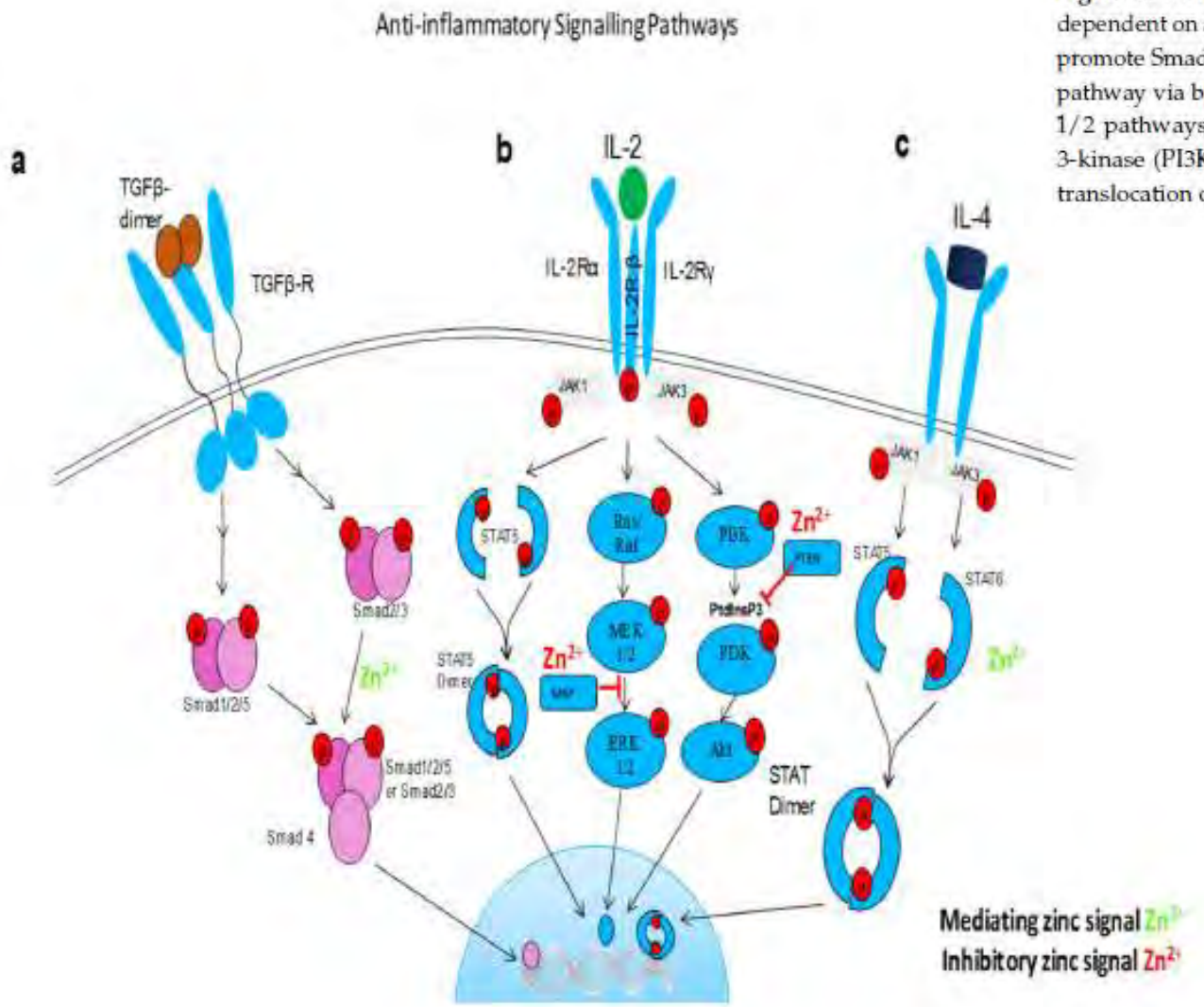
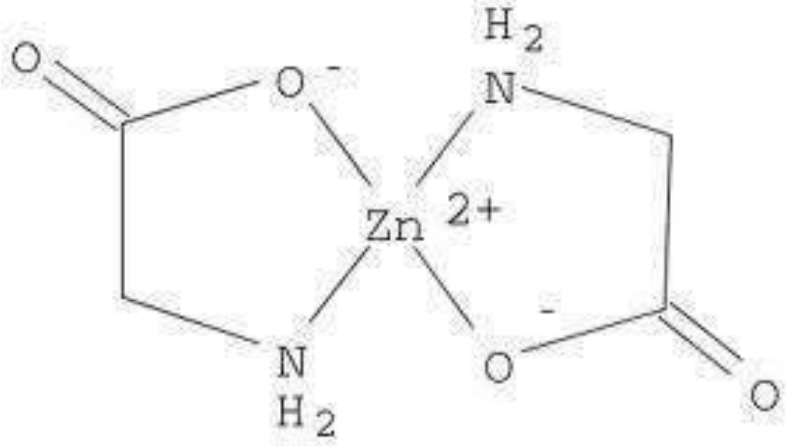


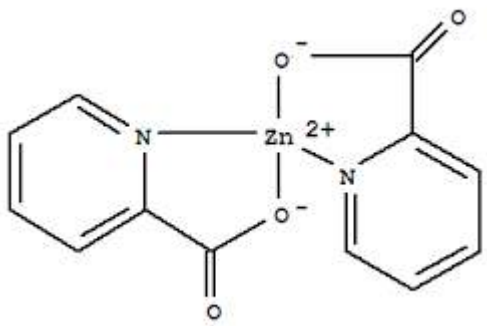
Figure 3. Anti-inflammatory signaling pathways influenced by free zinc. (**a**) TGFβ signaling is dependent on a dynamic on and off switch in Smad activity. Free zinc is a cofactor in Smad proteins and promote Smad 2/3 nuclear translocation and transcriptional activity. (**b**) zinc regulates IL-2 signaling pathway via blocking MAP kinase phosphatase (MKP) in extracellular signal-regulated kinases (ERK) 1/2 pathways and Phosphatase and tensin homologue (PTEN) which opposes phosphoinositide 3-kinase (PI3K) function in PI3k/Akt pathway. (**c**) free zinc phosphorylates STAT6 and promotes translocation of STAT dimers into the nucleus, hence promote the anti-inflammatory effects of Il-4.

Sali organici di Zinco

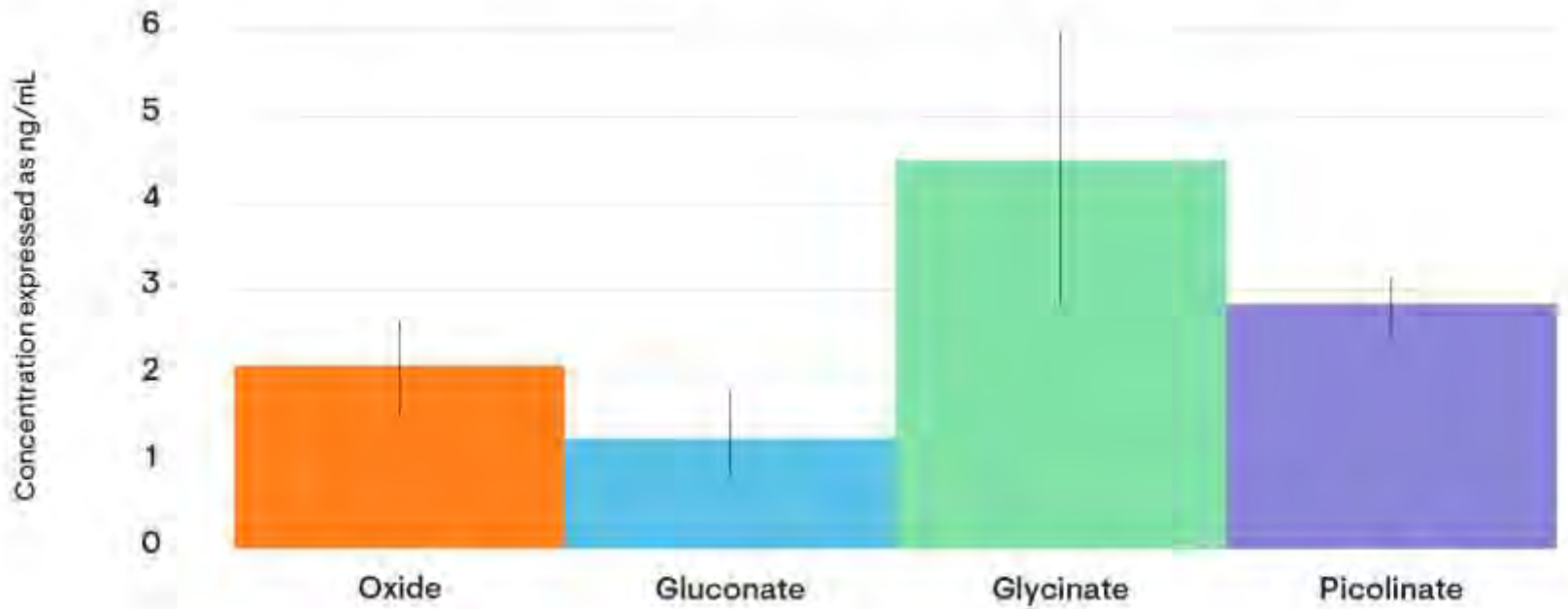
Chelati con amminoacidi come glicina o altri
Citrati, picolinati, gluconati, tartrati
Moltissime possibilità
Molto importante la solubilità
Zinco bisglicinato



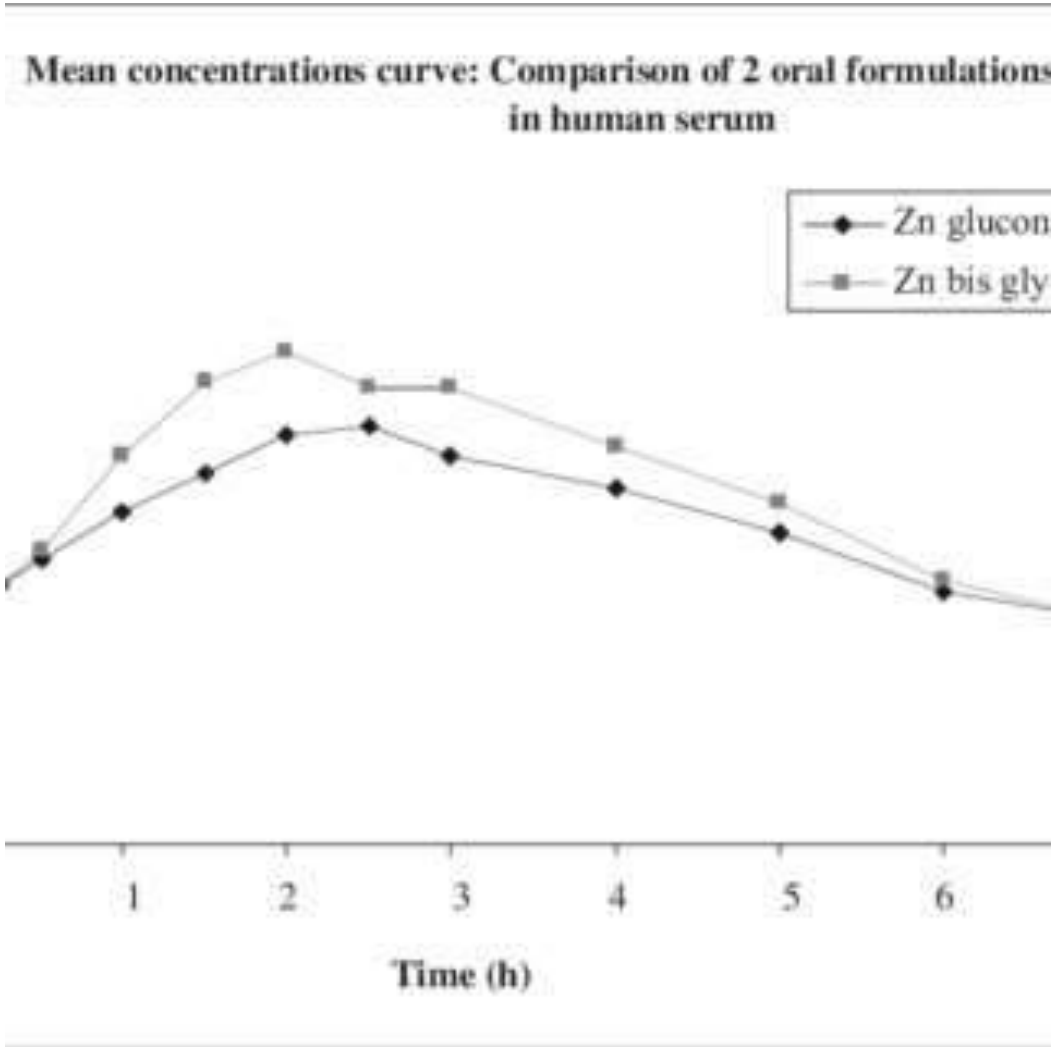
Zinco picolinato



Acute rise in RBC Zinc (Area under curve 0-4 h)



Glycinate value was different from all others, $P < 0.05$



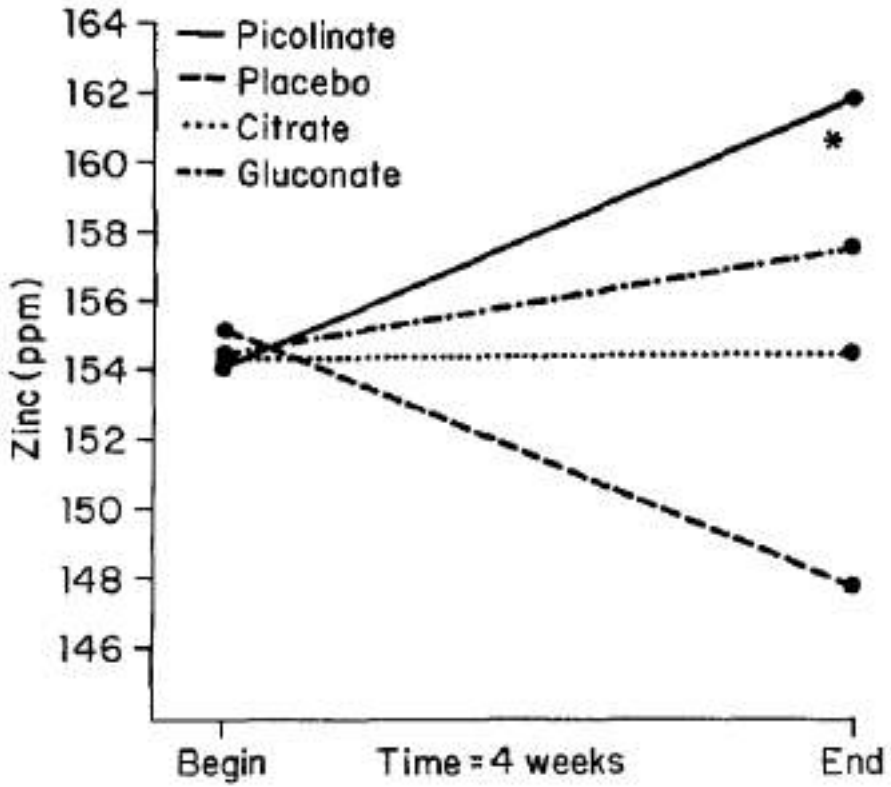


Figure 1
Changes in zinc level of hair after 4 weeks of supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo. Asterisk indicates significant change ($p < 0.005$).

Table 1
Zinc levels in human hair, urine, erythrocytes and serum before and after supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo.

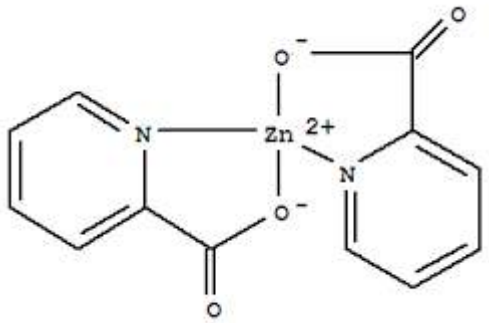
Supplement	Zinc levels (ppm) in			
	Hair	Urine	Erythrocytes	Serum
Zinc Picolinate				
Before	154.1±3.1	0.33±0.02	9.01±0.3	5.67±0.2
After	161.0 4.2	0.59 0.06	10.83 0.4	5.75 0.2
Mean Change	7.8* $	0.26* $	1.82*$	0.08
Placebo				
Before	155.7±3.9	0.35±0.06	9.32±0.4	5.07±0.1
After	147.5 3.9	0.31 0.04	8.53 0.3	5.49 0.2
Mean Change	−8.2	−0.04	−0.79	0.42
Zinc Citrate				
Before	154.7±5.4	0.34±0.04	9.09±0.5	5.43±0.1
After	154.8 4.5	0.33 0.06	9.44 0.4	5.64 0.2
Mean Change	0.1	−0.01	0.35	0.21
Zinc Gluconate				
Before	154.3±4.2	0.34±0.07	9.06±0.4	5.47±0.1
After	157.7 3.4	0.46 0.05	8.48 0.4	5.46 0.1
Mean Change	3.4	0.12	−0.58	−0.01

* Significant change ($p < 0.005$).
$ Significantly different from placebo ($p < 0.002$).
Values presented as Mean ± SEM ($n = 15$).

Funzioni sul sistema Immunitario

Antiossidante

Funzione su visione, olfatto, gusto



Ruolo nella sintesi proteica

Mantenimento dei corretti livelli di zuccheri

Unghie e capelli

Aiuta assorbimento delle vitamine B

Sistema riproduttivo

Controindicazioni Zinco

Soggetti con ipersensibilità specifica

Non superare l'RDA nelle donne in gravidanza e allattamento

Sopra i 30 mg/ giorno sono riportati effetti gastrointestinali o emicrania

L'assunzione cronica di zinco in quantità eccessive può portare ad una carenza di rame ed una anemia microcitica ipocromica secondaria alla carenza di rame indotta da zinco

Interazioni con farmaci e Zn

Riduzione di assorbimento di Bifosfonati

Riduzione assorbimento chinolonici e tetracicline

Da somministrare lontano da

Calcio (diminuisce assorbimento di zinco riportato per donne in post menopausa), attenzione anche con Sali fosfati

Acido ossalico, fitati, tannini (ad esempio da the) riduce assorbimento

Interazioni con farmaci e Zn

Cisteina, NAC, Metionina, proteine contenenti le precedenti possono aumentare assorbimento di zinco

Elevate dosi di zinco inducono sintesi di metallotionina che andrà però a sequestrare anche il Cu creando quindi una mancata disponibilità di rame nell'organismo

Sindrome di Wilson

Journal of Trace Elements in Medicine and Biology 71 (2022) 126942

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journal homepage: www.elsevier.com/locate/jtemb

Effect of zinc supplementation on circulating concentrations of homocysteine, vitamin B_{12}, and folate in a postmenopausal population

Introduction: The decrease in estrogen levels associated with menopause increases the risk of deficiencies of key micronutrients such as zinc and of disturbances in methylation cycle-related markers. The present study assesses the effect of 8-week Zn supplementation upon circulating concentrations of Hcy, B_{12}, and Fol levels in a population of postmenopausal women.

Methods: Fifty-one postmenopausal women aged between 44 and 76 years took part in the study. Two randomized groups (placebo and zinc [50 mg/day]) were treated during 8 weeks. Nutrient intake was assessed based on the 72-hour recall method. Zinc was analyzed by flame atomic absorption spectrophotometry. Clinical-nutritional parameters were determined by enzyme immunoassay techniques.

Results: Folate levels increased significantly ($p < 0.05$) in the zinc group on comparing the baseline versus follow-up values. Homocysteine decreased in the inter-group analysis ($p < 0.05$) after the intervention. Furthermore, higher folate ($r = -0.632$; $p = 0.005$) and vitamin B_{12} ($r = -0.512$; $p = 0.030$) levels were correlated to low homocysteine levels in the zinc group after the intervention, although the zinc intervention had the same effect on B_{12} levels in both groups.

Conclusion: Zinc supplementation enhanced circulating folate and homocysteine by improving the folate values in the zinc-supplemented group and decreasing homocysteine levels inter-groups. Further studies involving larger samples and optimizing the doses and intervention period are needed to reinforce our main findings.

Selenio

Elemento presente in tracce ma essenziale

Coinvolto nelle difese antiossidanti

Nella regolazione dell’ormone tiroideo

Nella regolazione dello stato ossidoriuttivo cellulare

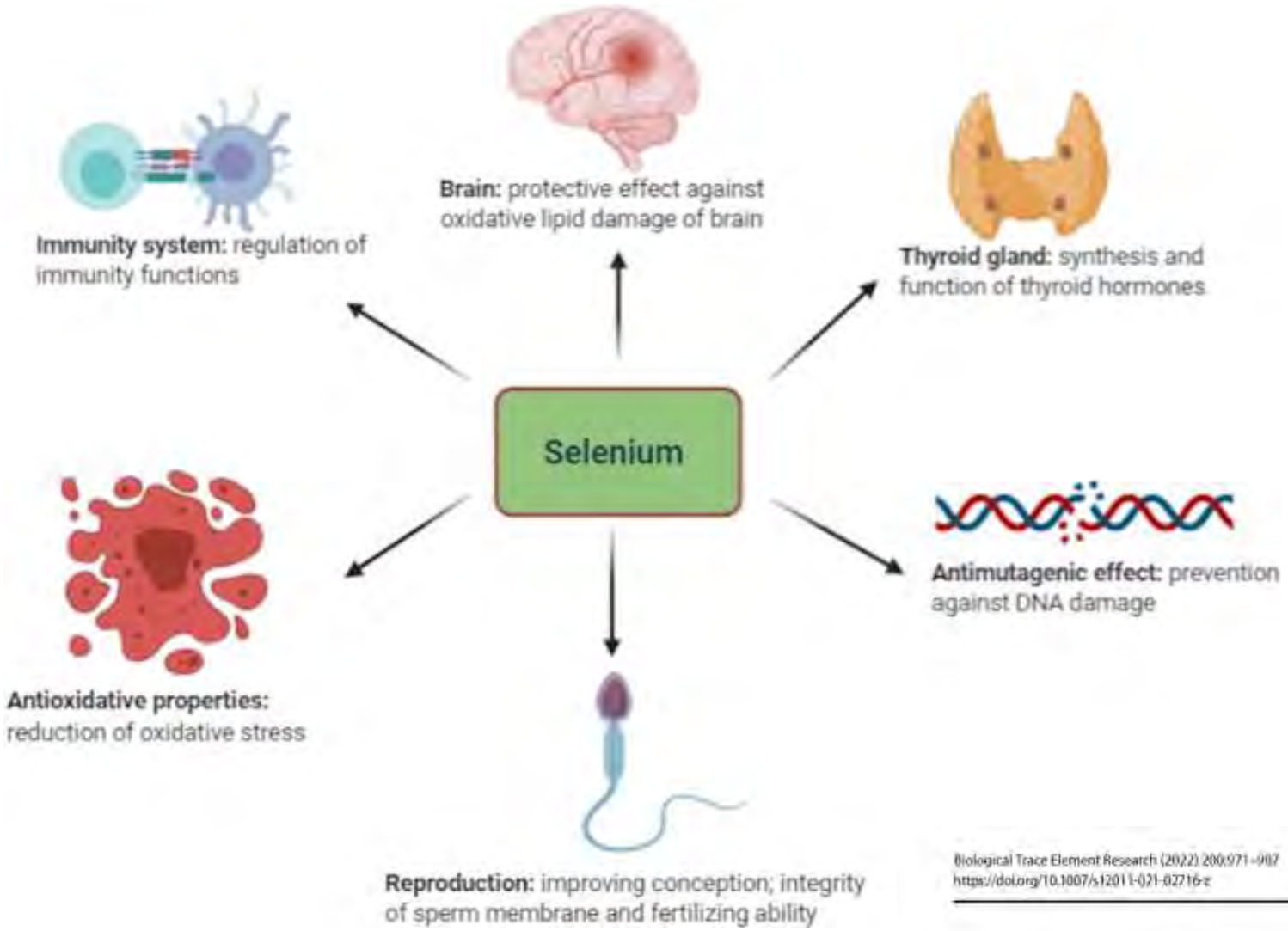
In alcune parti del mondo si ha una bassa quantità di selenio

Selenio

Marco Polo riporta di cavalli con distacco degli zoccoli perché si alimentavano di alcuni vegetali in particolari regioni della Cina (carenza)

Cardiomiopatia umana da carenza di Se (Descritta anni 70 Cina)

Kashin-Beck o malattia delle grandi articolazioni



Selenium and human health

Margaret P Rayman

www.thelancet.com Vol 379 March 31, 2012

Biological Trace Element Research (2022) 200:971–987
https://doi.org/10.1007/s12011-021-02716-z

A Comprehensive Review on Selenium and Its Effects on Human Health and Distribution in Middle Eastern Countries

Marek Kieliszek[1] · Iqra Bano[2] · Hamed Zare[3]

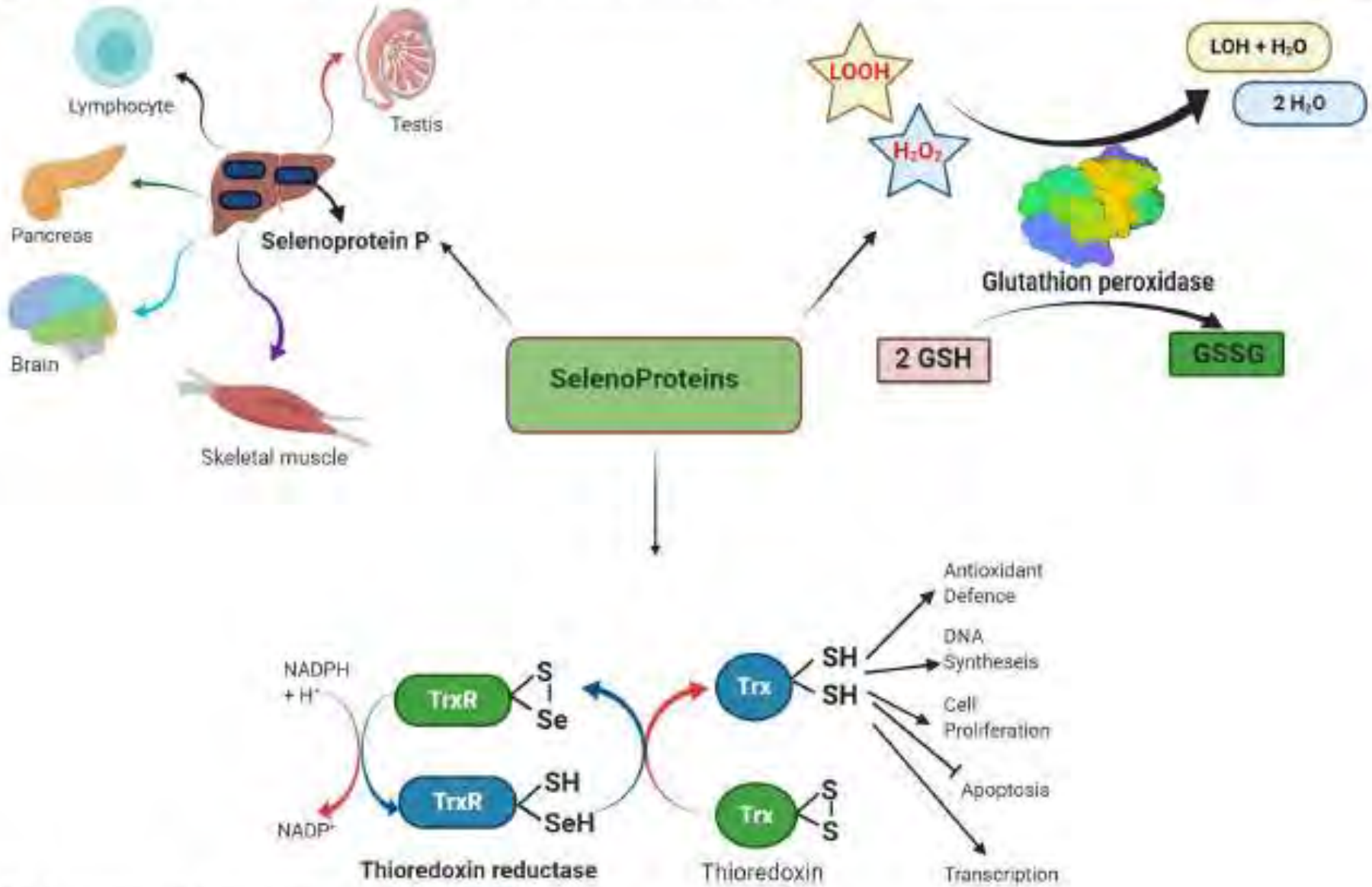
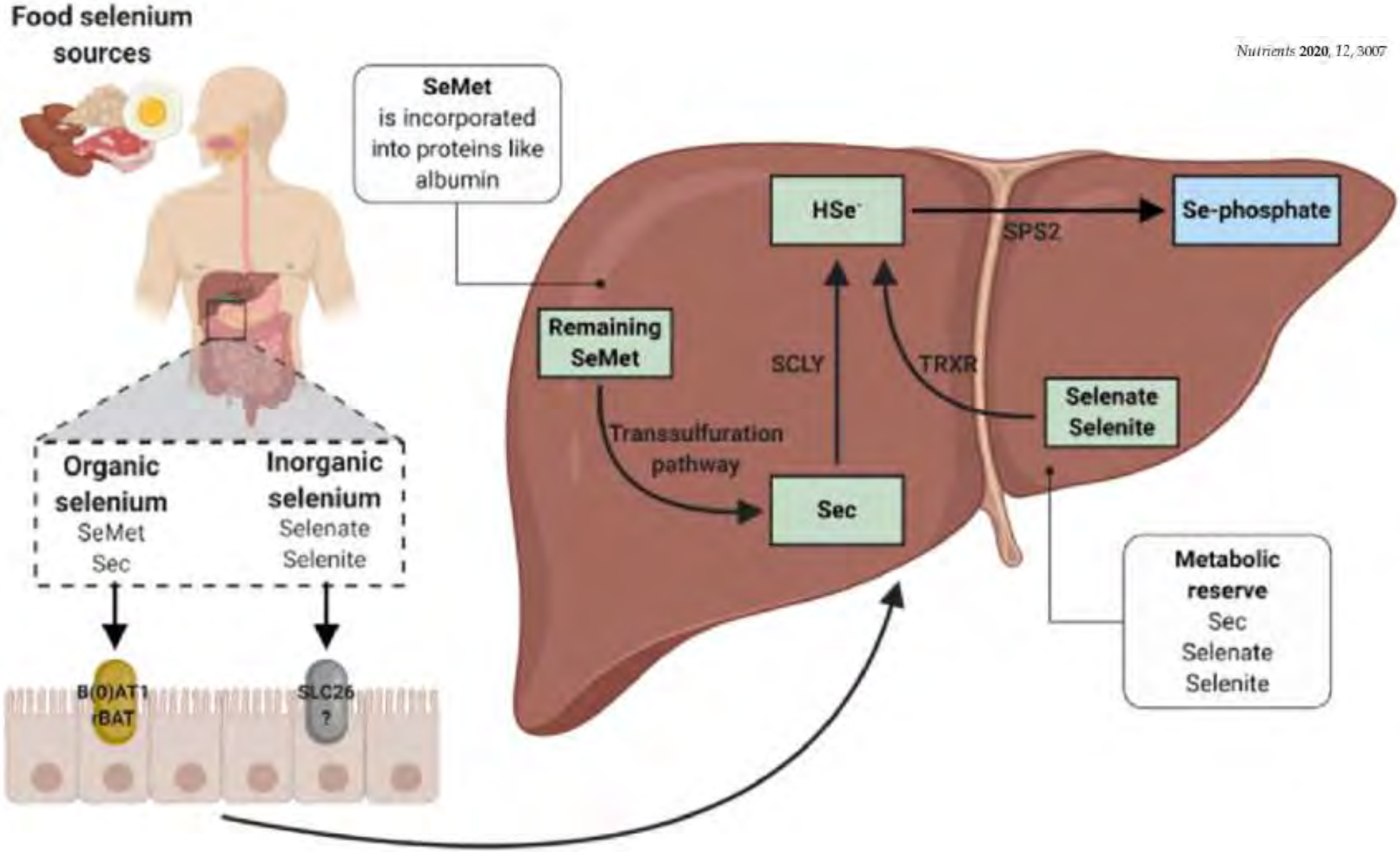
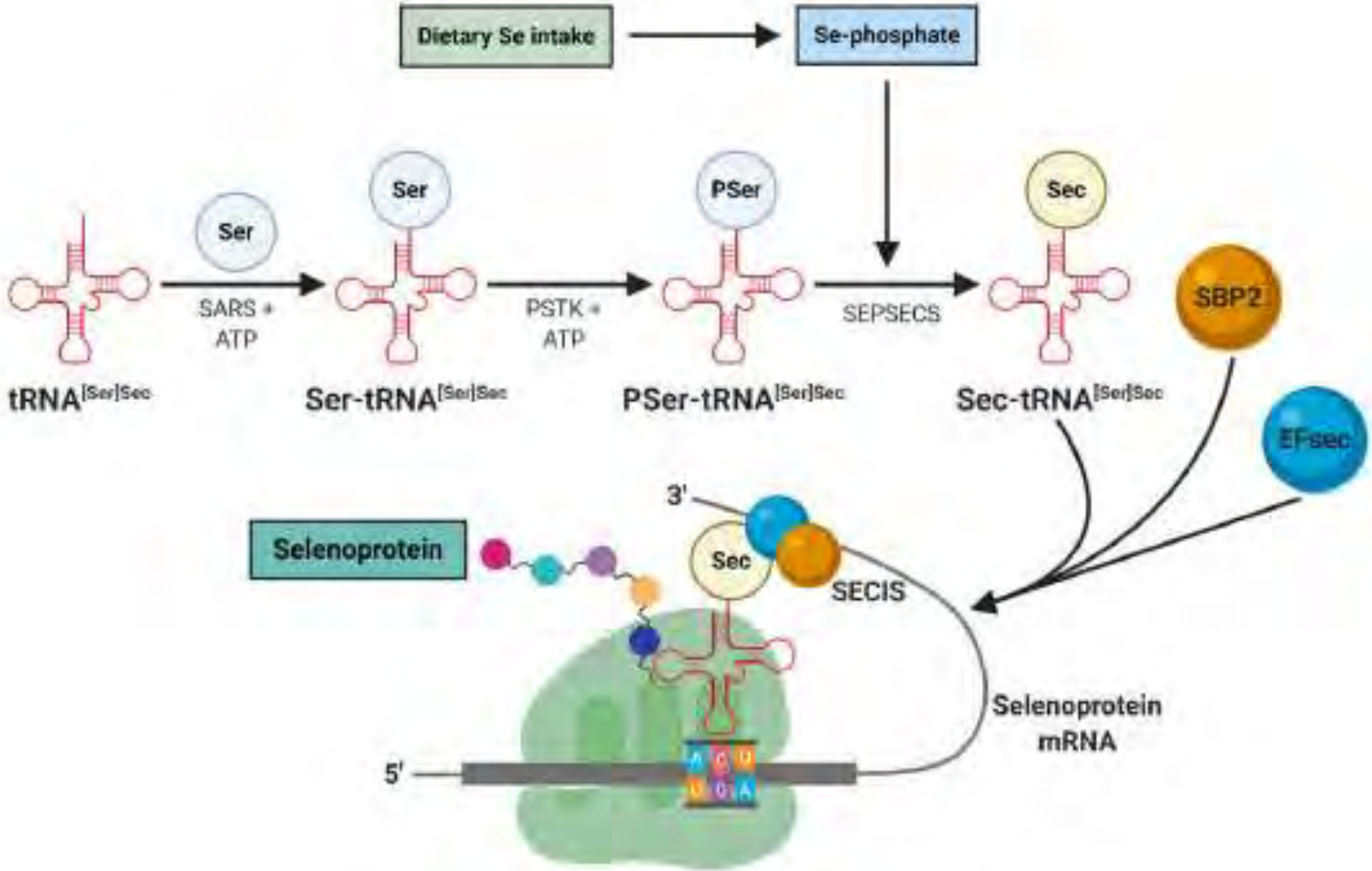


Fig. 2 Examples of selenoproteins and their functions in organisms


Food selenium sources
SeMet is incorporated into proteins like albumin
Organic selenium
SeMet
Sec
Inorganic selenium
Selenate
Selenite
B(0)AT1
rBAT
SLC26
?
Remaining SeMet
Transsulfuration pathway
Sec
SCLY
HSe⁻
SPS2
Se-phosphate
TRXR
Selenate
Selenite
Metabolic reserve
Sec
Selenate
Selenite


Dietary Se intake
Se-phosphate
Ser
Ser
SARS + ATP
Ser
PSer
PSTK + ATP
SEPSECS
Sec
SBP2
EFsec
tRNA[Ser]Sec
Ser-tRNA[Ser]Sec
PSer-tRNA[Ser]Sec
Sec-tRNA[Ser]Sec
3'
Selenoprotein
Sec
SECIS
Selenoprotein mRNA
5'

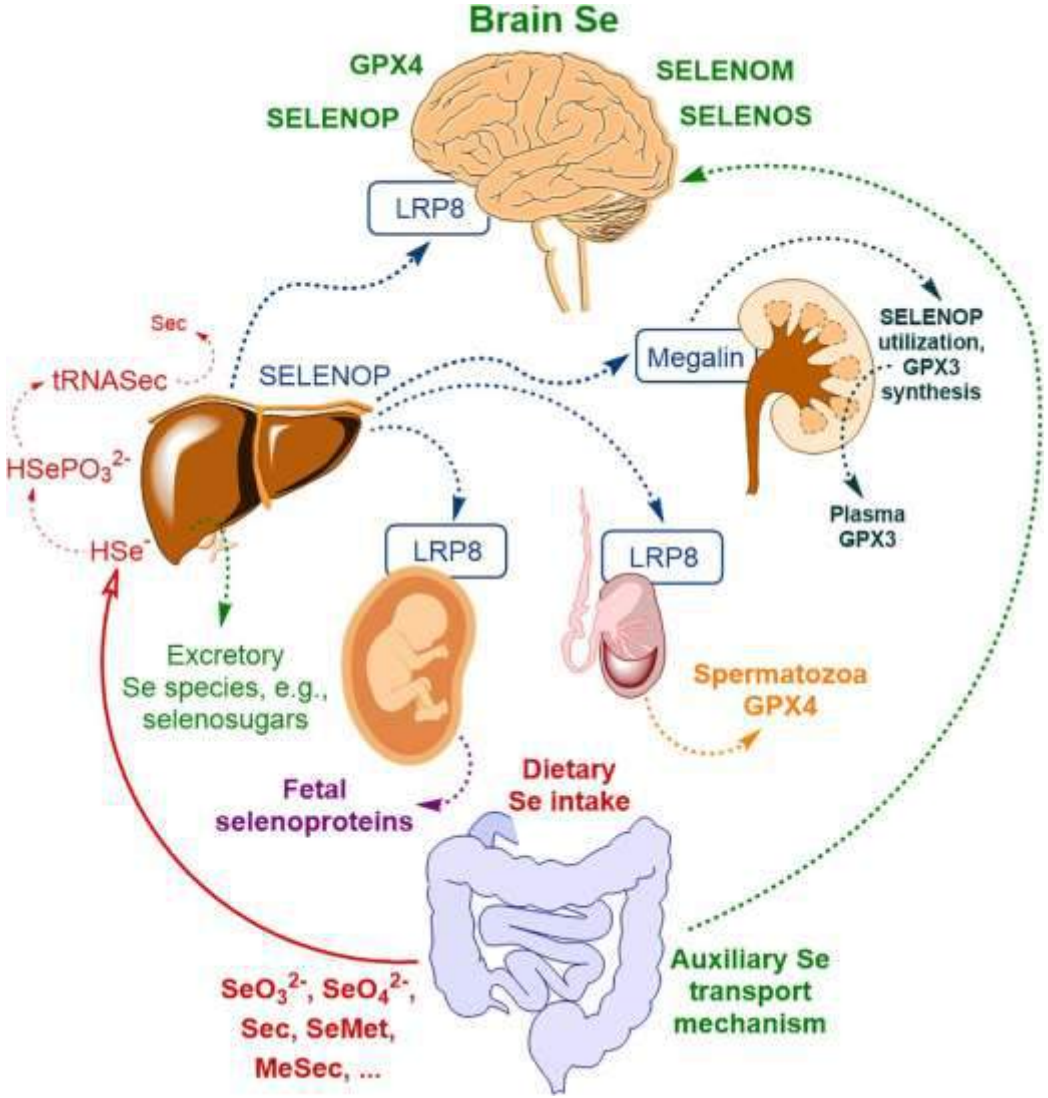


FIGURE 1 | The scheme of body Se homeostasis. Abbreviations: LRP8 – low-density lipoprotein receptor-related protein 8 (LRP8, also known as apolipoprotein E receptor-2, ApoER2), GPX3 – glutathione peroxidase type III, GPX4 – glutathione peroxidase type IV, Sec – selenocysteine, MeSec – methyl selenocysteine, SELENOM – selenoprotein M, SELENOP – selenoprotein P, SELENOS – selenoprotein S; * – auxiliary brain Se transport mechanism, independent of SELENOP, possibly related to selenosugars (Burk and Hill, 2015) and other low molecular weight Se-species (Solovyev et al., 2013) and possibly other minor contributors (please, see text for more detail). Based on Solovyev et al. (2018) with modification.

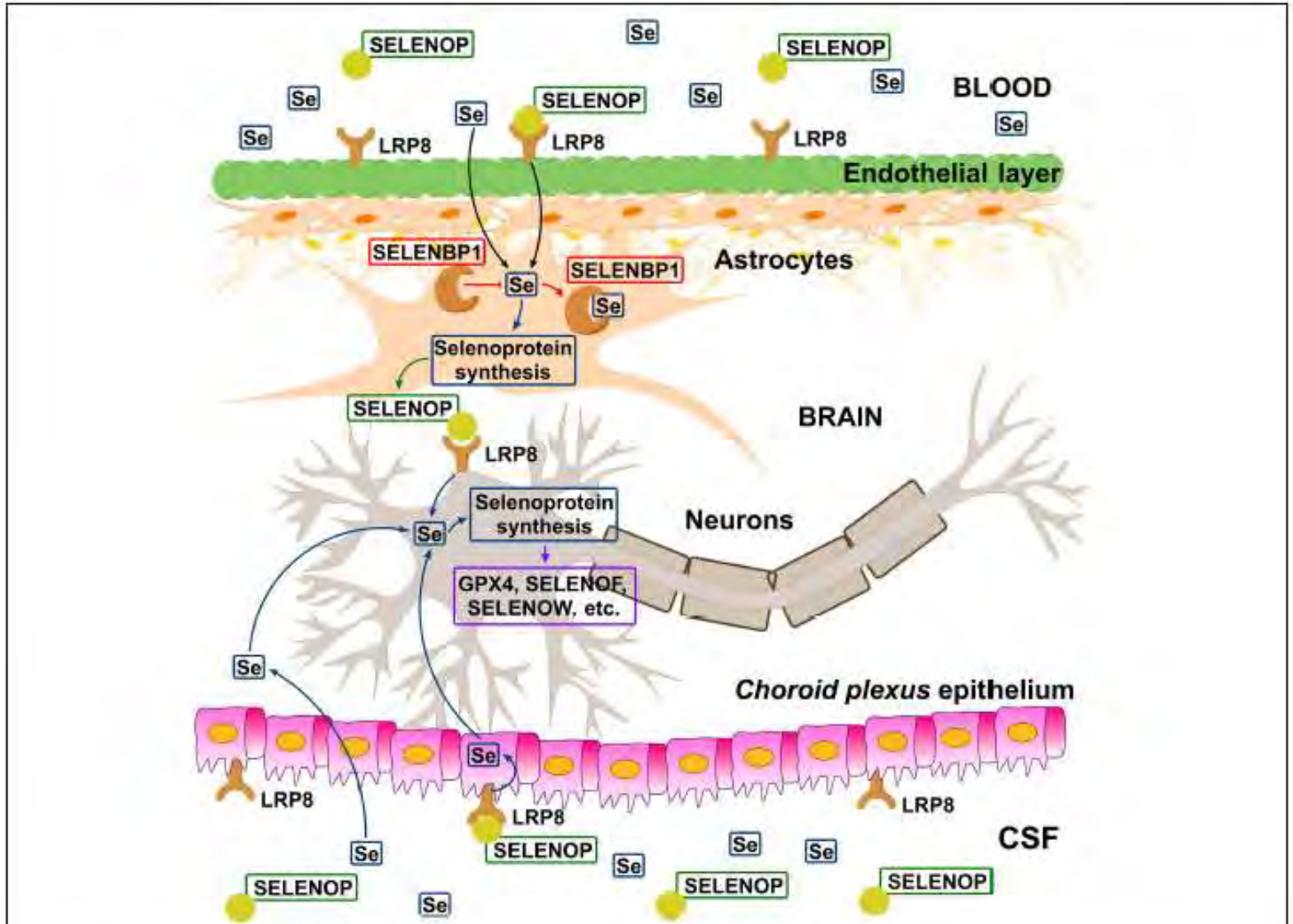


FIGURE 2 | Hypothetical model of Se transport across blood–brain barrier (BBB) and blood–cerebrospinal fluid barrier (BCB). Circulating SELENOP present in blood and CSF is taken up by LRP8-positive cells in the epithelial (BBB) and ependymal (BCB) layers, resynthesized in neighboring astrocytes, and released to supply LRP8-positive neurons with Se. In the astrocytes, SELENBP1 sequesters Se from selenoprotein synthesis and thus negatively regulating SELENOP production. There is also evidence indicating the existence of the SELENOP-independent Se uptake pathway (**Figure 1**). Reproduced from Sasuclark et al. (2019) with modification.

Kang et al. *Experimental & Molecular Medicine* (2020) 52:1198–1208
https://doi.org/10.1038/s12276-020-0408-y

Experimental & Molecular Medicine

REVIEW ARTICLE Open Access

The role of selenium metabolism and selenoproteins in cartilage homeostasis and arthropathies

Donghyun Kang[1,2], Jeeyeon Lee[1,2], Cuiyan Wu[3], Xiong Guo[3], Byeong Jae Lee[2,4], Jang-Soo Chun[2,4] and Jin-Hong Kim[1,2,4]

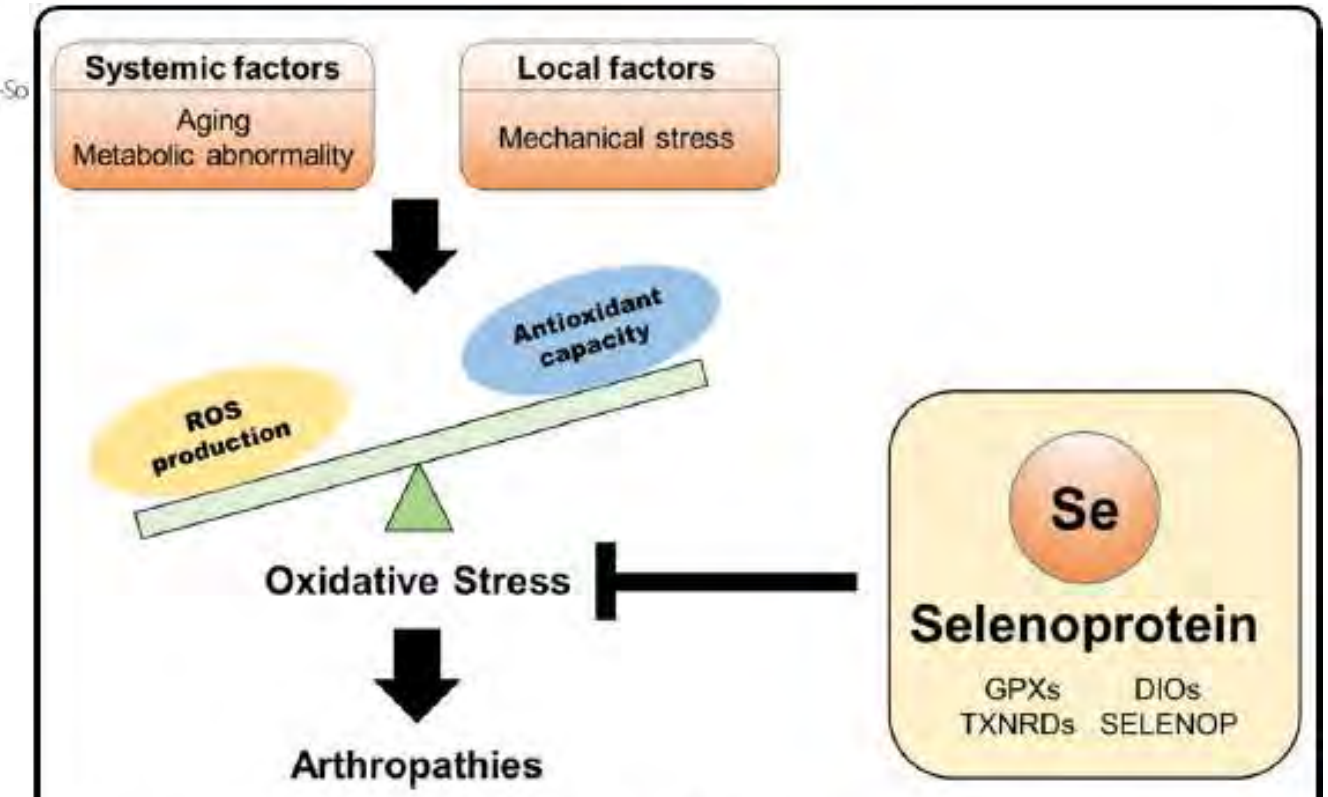


Fig. 2 The protective function of selenoproteins against imbalanced redox homeostasis and the progression of arthropathies. Oxidative stress induced by systemic and local factors

Supplementazione di selenio

Selenato e selenito di sodio (forme inorganiche)

L-selenometionina forma organica di selenio è

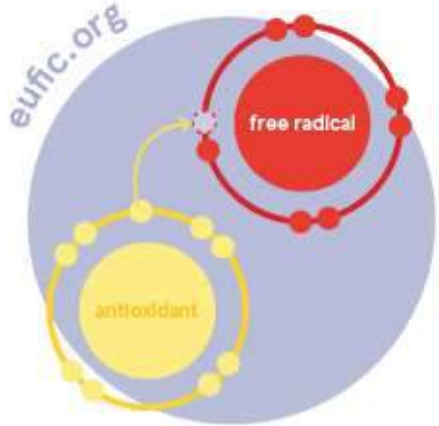
l’amminoacido corrispondente a metionina

Lieviti ad elevato titolo di selenio (come selenometionina)

Selenio-metilselenocisteina è la forma che si trova

nell’aglio

functions of selenium

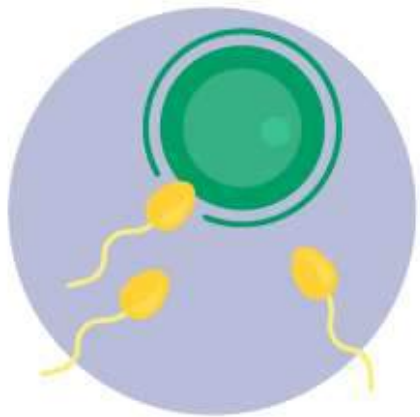


protects our cells against damage from free radicals

supports our immune system

grows & keeps healthy muscles

support our thyroids' function



supports our reproduction

DIREZIONE GENERALE PER L'IGIENE E LA SICUREZZA DEGLI ALIMENTI E LA NUTRIZIONE

UFFICIO 4

Apporti giornalieri di vitamine e minerali
ammessi negli integratori alimentari
Revisione aprile 2019

MINERALI	UNITA' DI MISURA	APPORTO MASSIMO	DISPOSIZIONI
Calcio	mg	1200	
Fosforo	mg	1200	
Magnesio	mg	450	
Ferro	mg	30	
Zinco	mg	15 per prodotti destinati agli adulti 7,5 per prodotti destinati a bambini (a partire da 3 anni) e adolescenti	Per prodotti eventualmente destinati alla prima infanzia (fino a 3 anni) non può comunque essere superato il VNR di 5 mg (da direttiva 2006/141/CE)
Rame	mg	2	
Manganese	mg	10	
Fluoro	mg	4	Per il fluoro, considerati i fabbisogni dei bambini entro i tre anni di età, è ammesso un apporto minimo pari a 0,25 mg pur se inferiore al 15% del VNR.
Selenio	µg	100	
Cromo	µg	200	
Molibdeno	µg	100	
Iodio	µg	225	
Boro	mg	3,6	Per il boro, per il quale non è previsto un VNR, l'apporto minimo non deve essere inferiore a 0,23 mg.

SELENIUM

Oregon State University
Linus Pauling Institute

MAIN FUNCTIONS

- Assists antioxidant enzymes
- Needed for production of thyroid hormone, which helps maintain body temperature and basal metabolic rate
- Supports immune function

GOOD SOURCES

Meat, nuts, seafood, and whole grains are good sources of selenium.

Meat

beef · chicken · pork

- Beef, 3 ounces, 30.6 µg

Nuts

Brazil nuts · sunflower seeds

- Sunflower seeds, ¼ cup, 18.6 µg

Seafood

tuna · clams · shrimp

- Tuna, 3 ounces, 92.0 µg

µg = micrograms; a 3-ounce serving of meat or fish is about the size of a deck of cards

DAILY RECOMMENDATION

55 µg

Adults

SPECIAL NOTES

- The selenium content of plants and grains varies greatly.
  - » Food selenium content is influenced by the selenium content of the soil in which it was grown.
  - » Some plants accumulate selenium to a greater extent, including garlic, Brazil nuts, and *Brassica* vegetables (broccoli, Brussel sprouts, cabbage, cauliflower, kale).
  - » A single serving of Brazil nuts (6 nuts) is above the tolerable upper intake level (UL) of 400 µg/day.
- Most people in the US consume enough selenium to meet the recommendation.

Controindicazioni Selenio

Soggetti con ipersensibilità specifica

Non superare l'RDA nelle donne in gravidanza e allattamento

Selenosi è tossicità da assunzione cronica elevata fragilità capelli e unghie

arrossamento cute affaticamento

Dosi da 50 ug/die come Se fino a 200 ug/die non di più