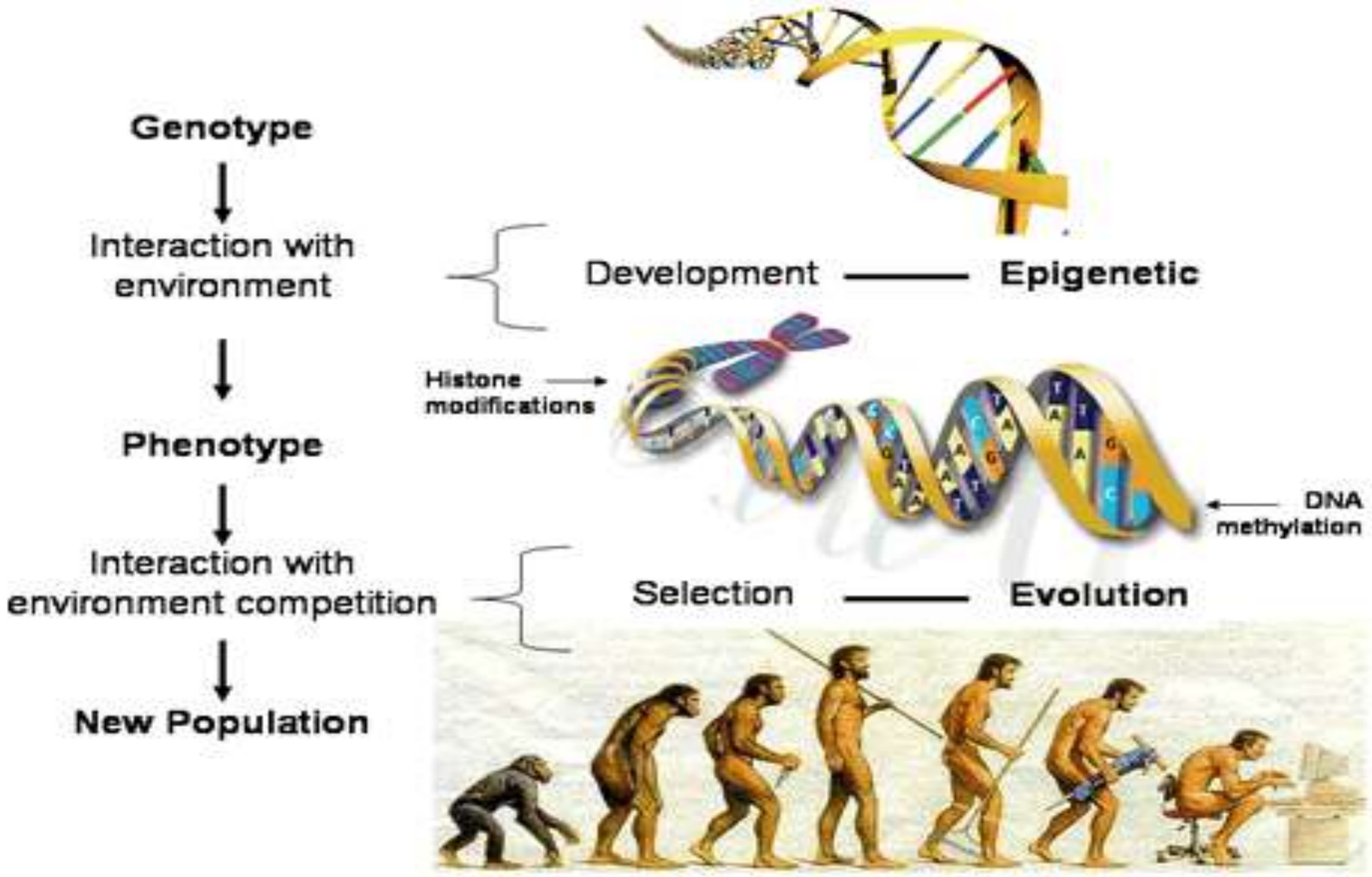
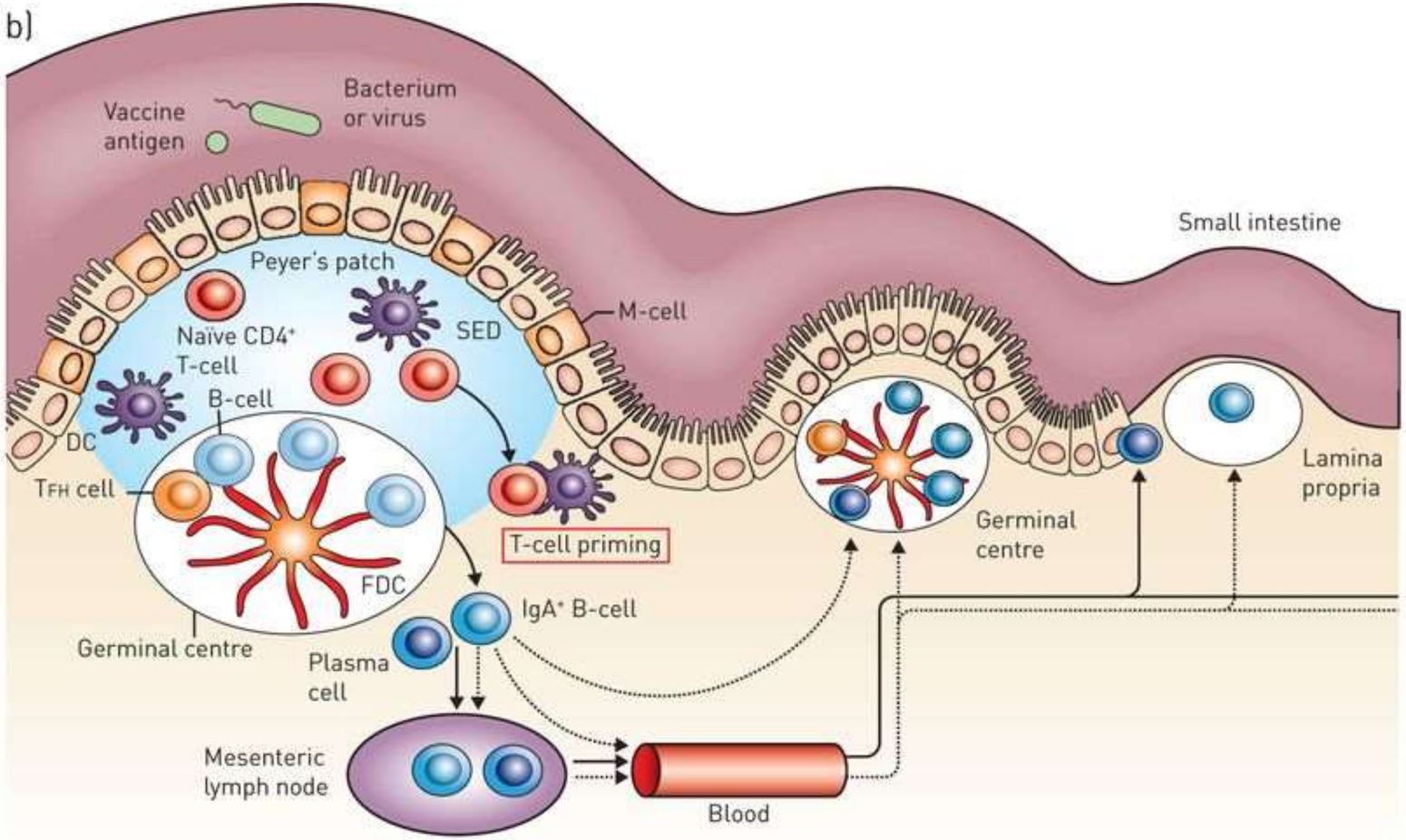
Uloga probiotika, vitamina D i cinka u lečenju COVID-a i hroničnih bolesti

Prof. dr Borislav Kamenov

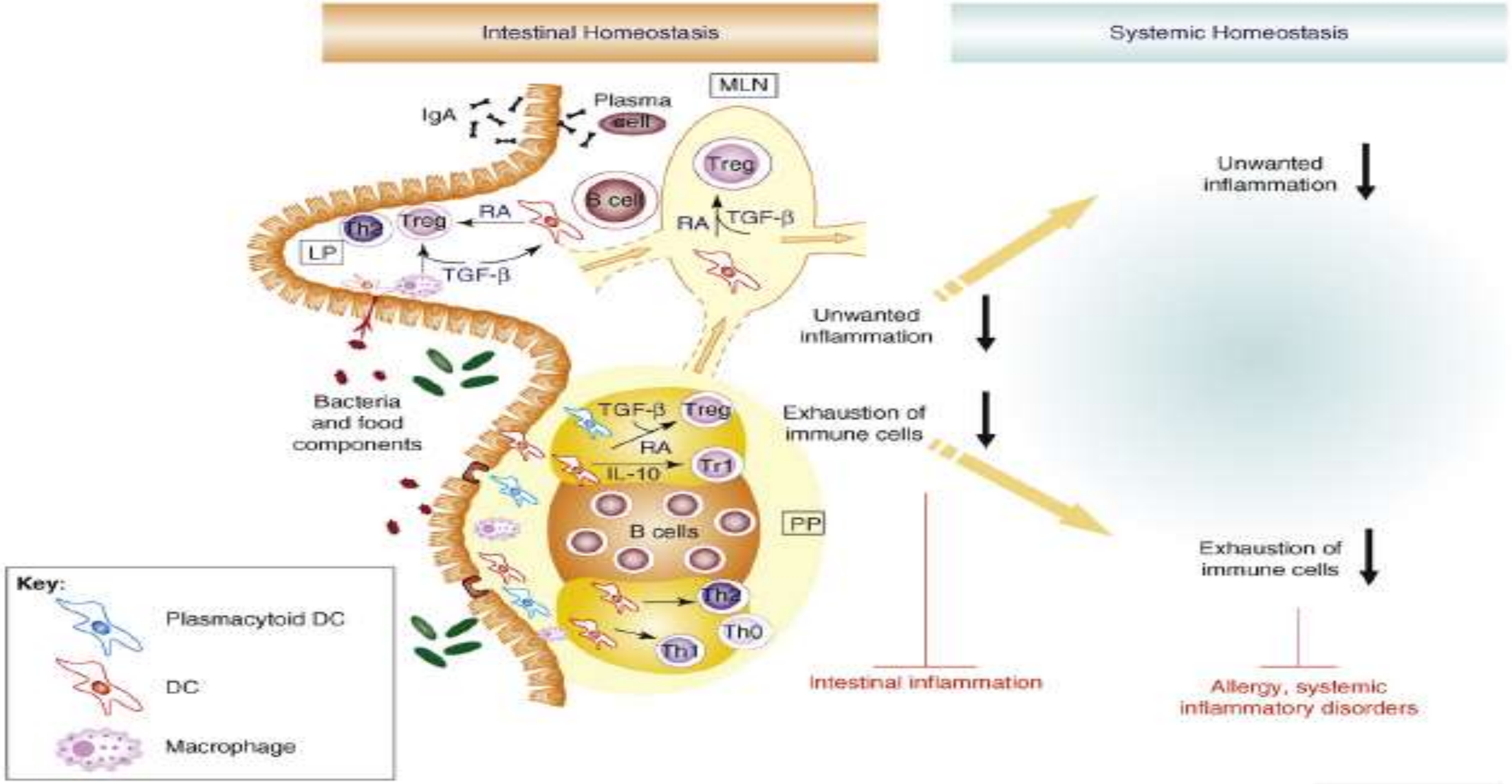
Evolucija i epigenetika



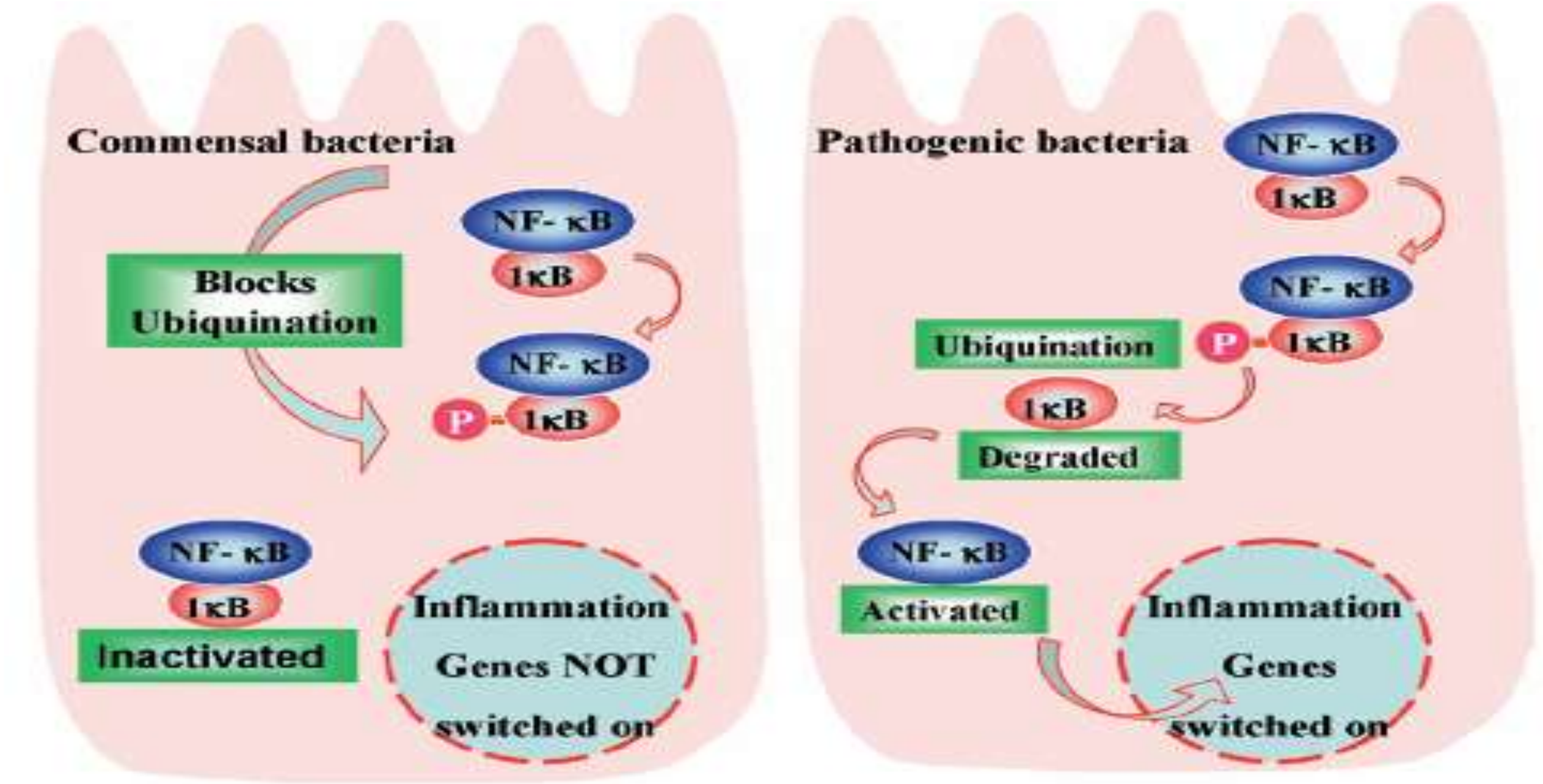
Digestivni trakt i razvoj imunskog sistema



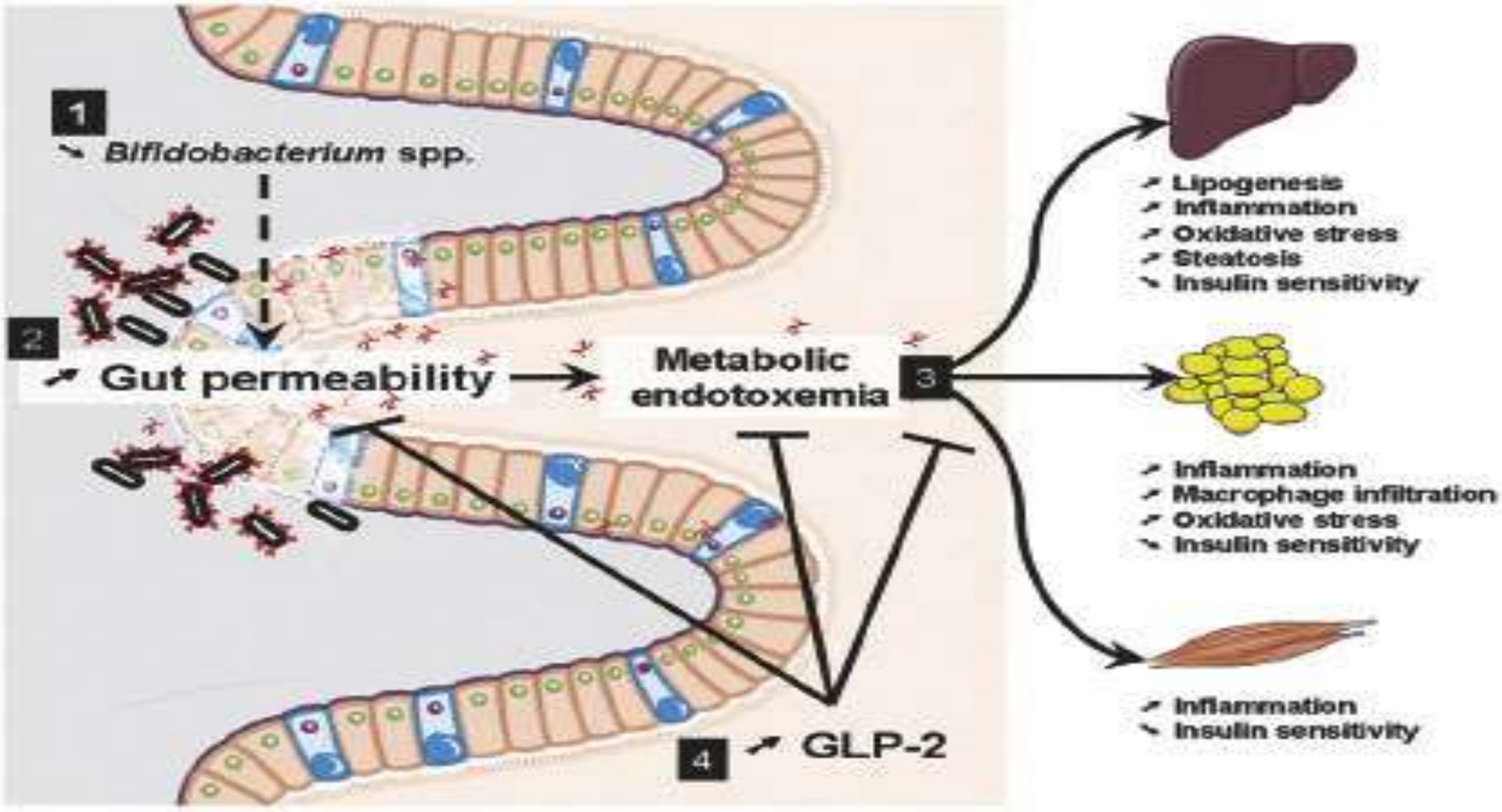
Oralna tolerancija: fiziološka avenija ka intestinalnoj i sistemskoj homeostazi regulatornih t ćelija



Efekat commensalnih i patogenih bakterija na inflamaciju

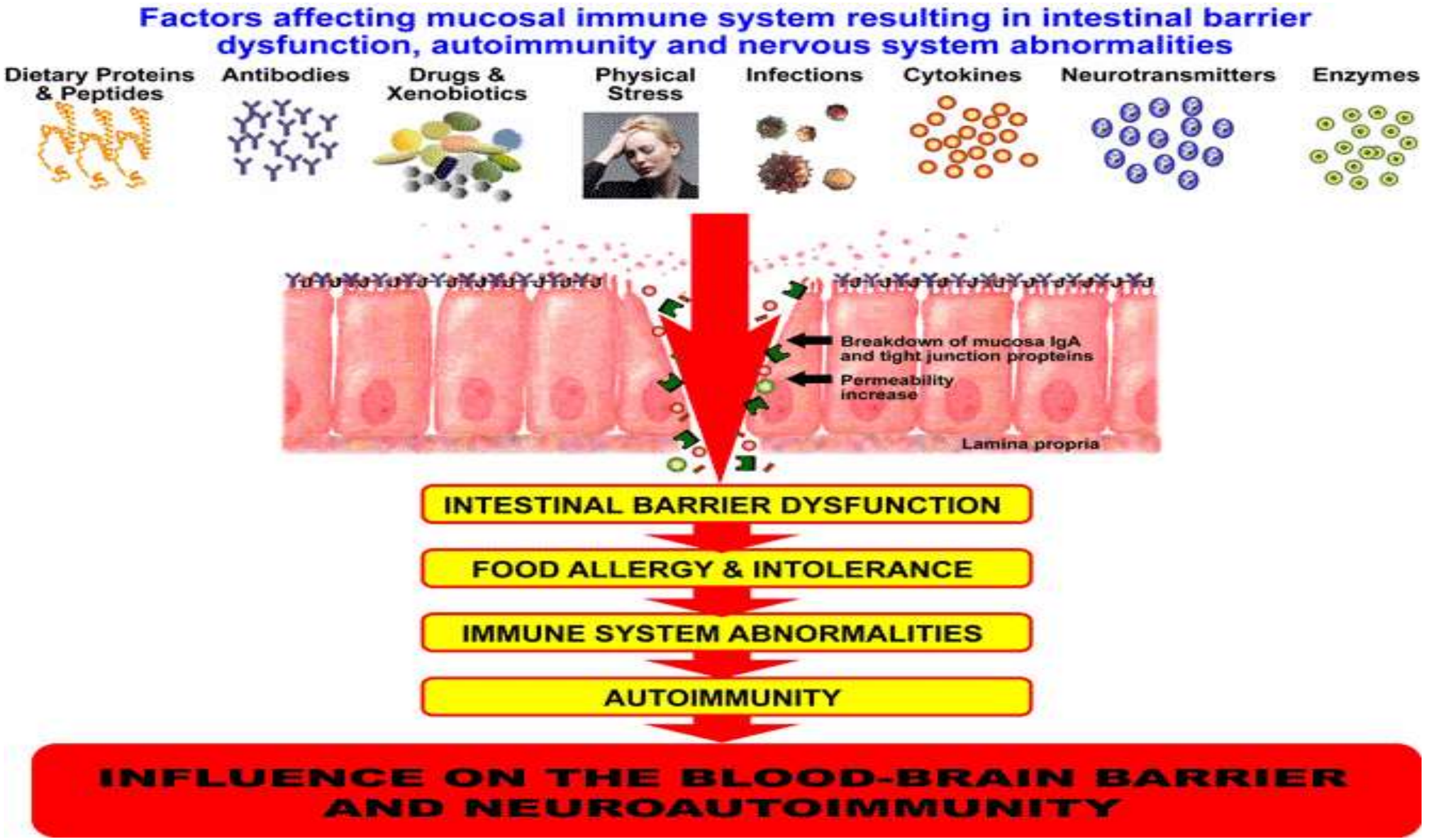


Propustljivost creva i metabolička endotoksemija




YOUR GUT LINING IS DISTURBED
too much alcohol consumption
too much stress/ lack of sleep
too many antibiotic prescriptions
not enough fatty acids in the diet
use of NSAIDs
viral infection occurs
1
YOUR GUT ABSORBS NUTRIENTS IMPROPERLY
you are fatigued
your body begins to get bloated
2
YOU DEVELOP AN AUTOIMMUNE DISORDER
rheumatoid arthritis
lupus
celiac disease
Crohn's disease
fibromyalgia
ulcerative colitis
6
What can happen when a patient suffers from Dysbiosis, a disturbance in the balance of bacterial flora in their gastrointestinal tract?
http://healthy-family.org
5
3
4
YOU DEVELOP MULTIPLE FOOD INTOLERANCES
headaches
IBS
eczema
asthma
constipation
diarrhea
YOU DEVELOP A LEAKY GUT
holes in the intestinal lining cause symptoms:
excessive gas
cramps
joint pain
skin rashes
vaginal infections
YOUR GUT BECOMES INFLAMED
food particles are leaked from the gut
nutrients are not absorbed
IgG antibodies are produced
chemical sensitivities

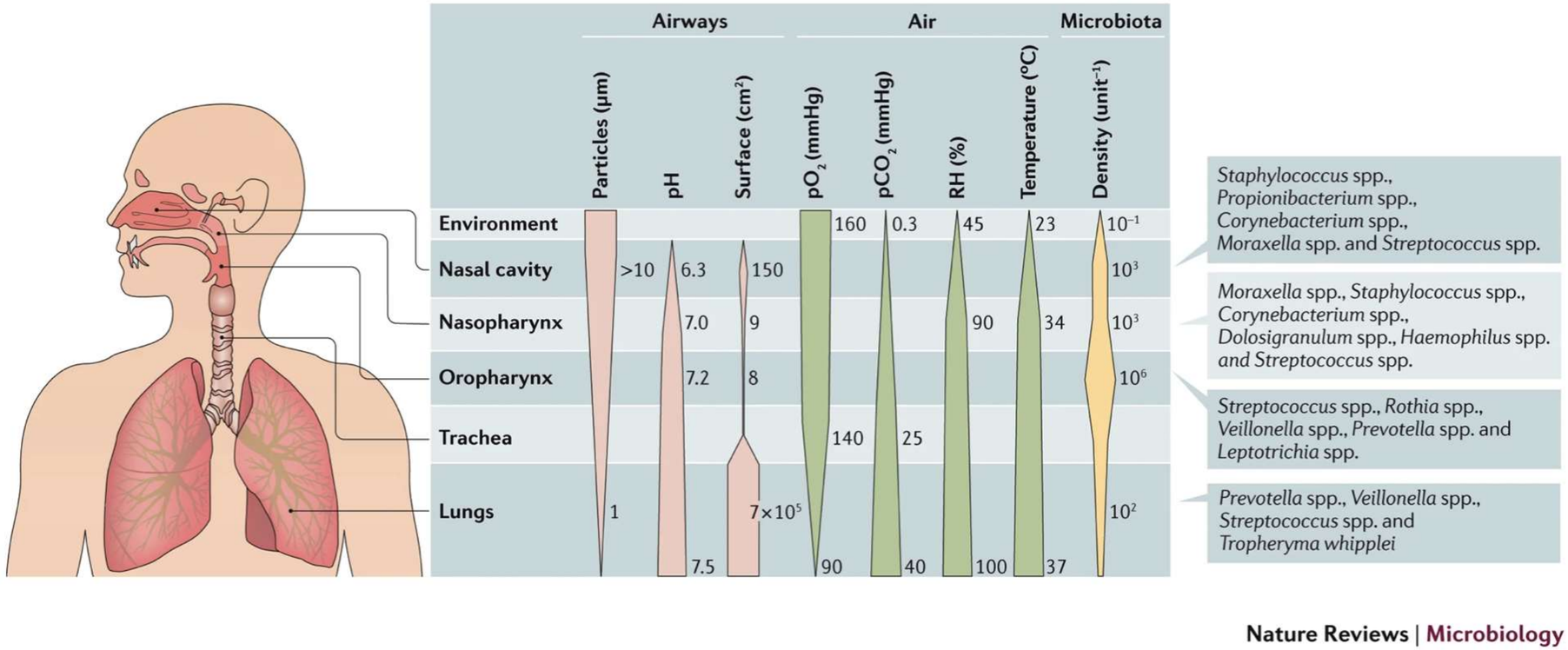
Faktori koji utiču na imunski sistem mukoze



Mikrobiota respiratornog trakta: čuvar zdravlja disajnih puteva

Figure 1: Physiological and microbial gradients along the respiratory tract.

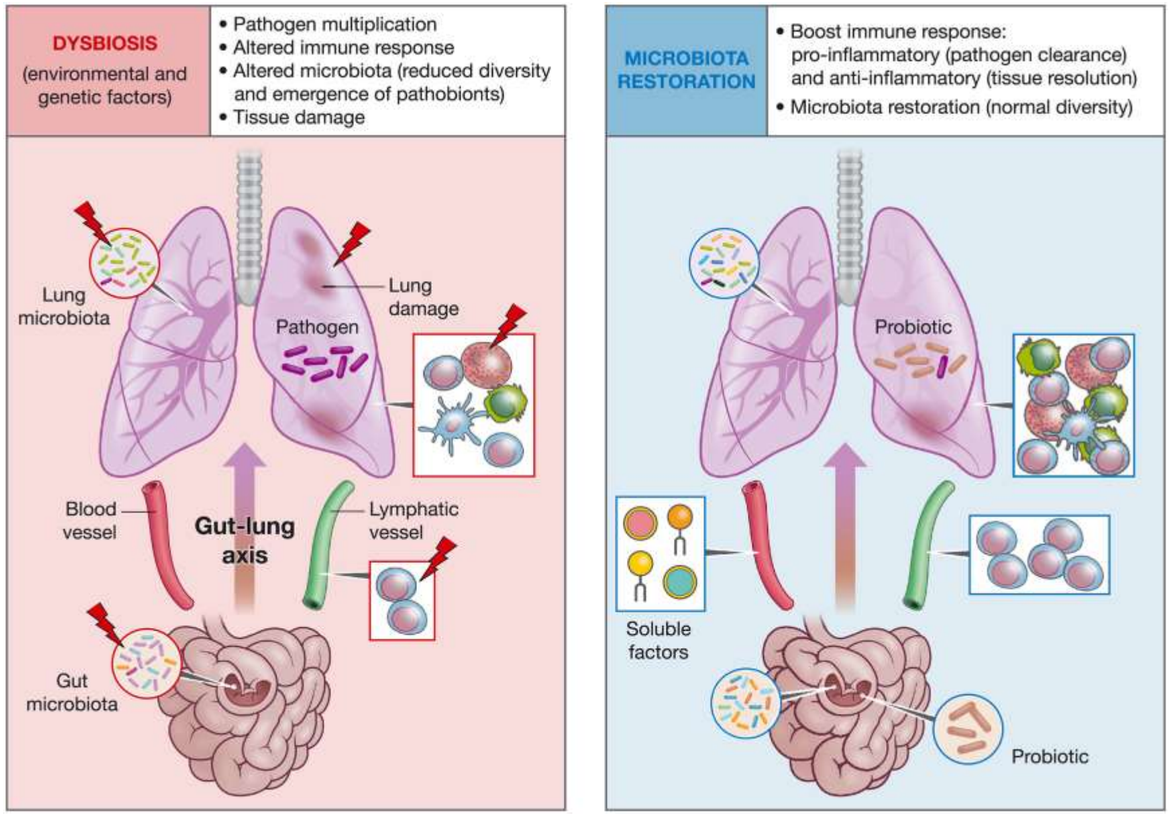
From: The microbiota of the respiratory tract: gatekeeper to respiratory health



Man, W., de Steenhuijsen Piters, W. & Bogaert, D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol* **15**, 259–270 (2017). https://doi.org/10.1038/nrmicro.2017.14

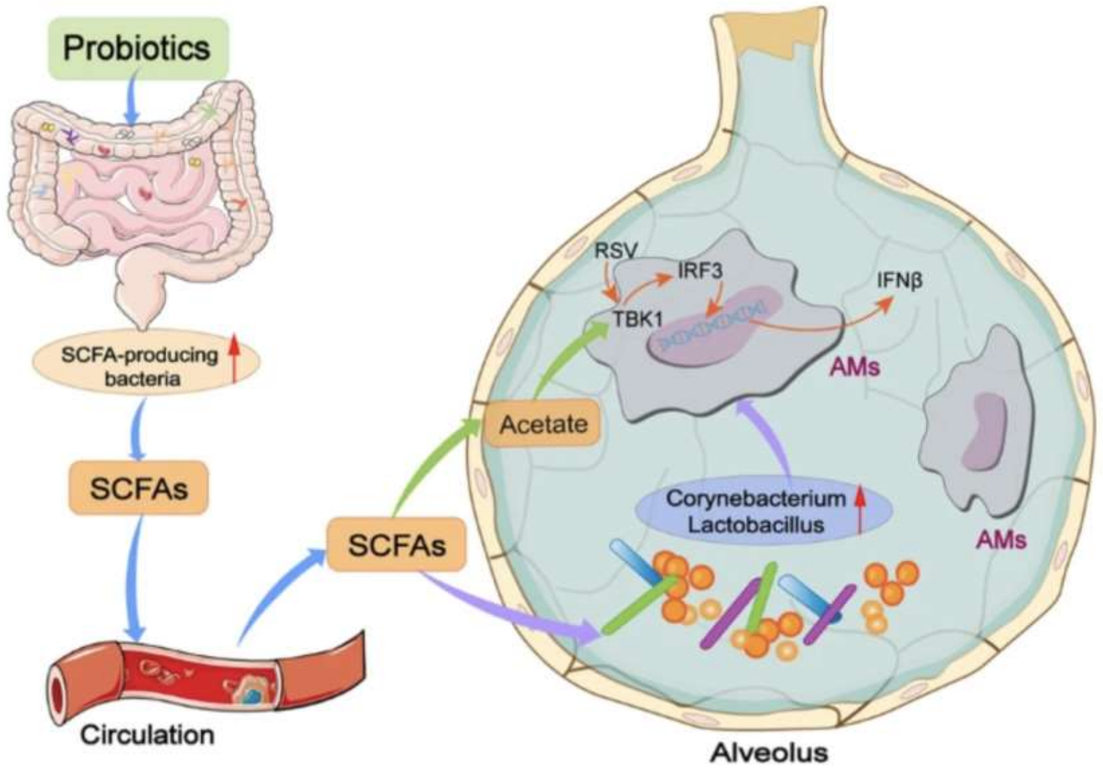
Veza mikrobiote pluća i intestinalnog sistema

- Mezenterijalni limfni sistem je osnovni put između pluća i creva
- Mikrobiota pluća utiče na imunitet sluznica i doprinosi imunološkoj toleranciji.
- Disbioza intestinalnog sistema dovodi do izmenjenog imunskog odgovora: alergijskih reakcija ili smanjenja klirensa patogena



Dumas A, Bernard L, Poquet Y, Lugo-Villarino G, Neyrolles O. The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. Cellular Microbiology. 2018;20:e12966. https://doi.org/10.1111/

Probiotici štite od respiratornih infekcija modulacijom ose mikrobiota-alveole-makrofazi[1].

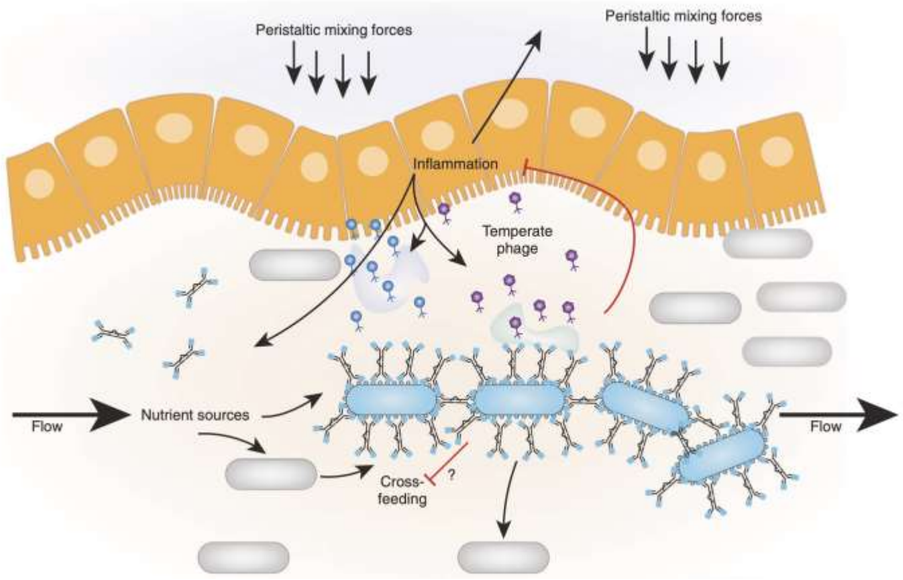


Studija je pokazala da probiotici štite od RSV infekcije kod tek rođenih miševa preko mikrobiota-alveole-makrofazi ose, što sugeriše da probiotici mogu biti obećavajući kandidati za sprečavanje i tretman RSV infekcije.

Ji, Jj., Sun, Qm., Nie, Dy. *et al.* Probiotics protect against RSV infection by modulating the microbiota-alveolar-macrophage axis. *Acta Pharmacol Sin* **42**, 1630–1641 (2021). https://doi.org/10.1038/s41401-020-00573-5

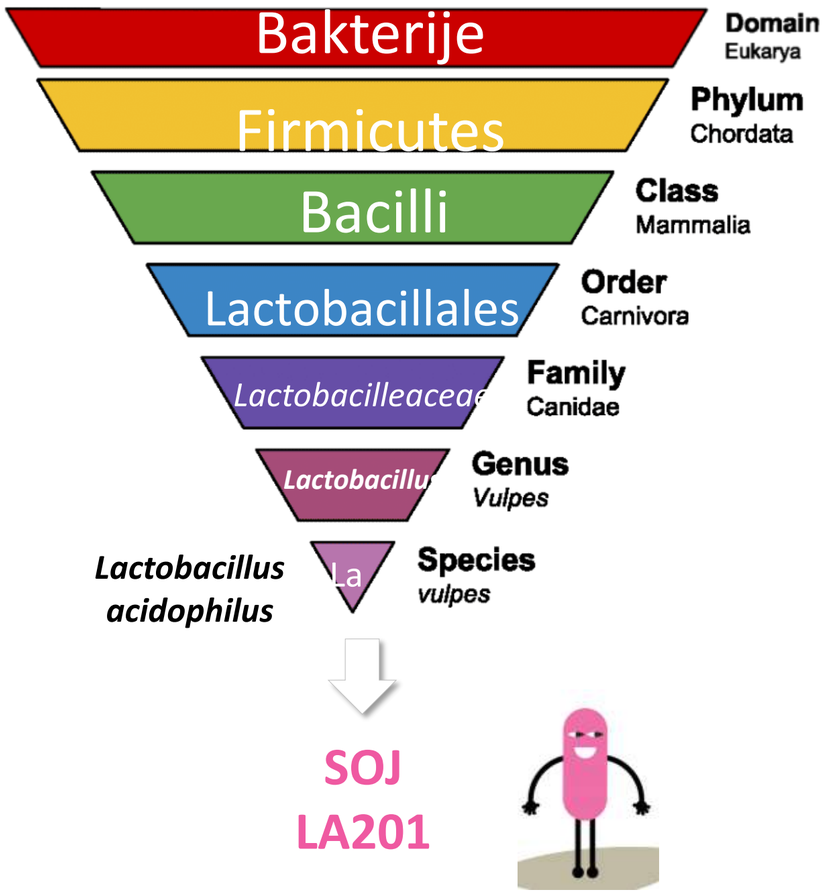
sIgA i intestinalna mikrobiota

- Bakterijski antigeni intestinalne mikrobiote podstiču proizvodnju **sIgA.**
- **IL-10** je važan u održavanju tolerancije sluznica.
- **Sekretorna IgA (sIgA) antitela:**
  - Regulišu kolonizaciju mikroorganizama na sluznicama.
  - Inhibiraju penetraciju potencijalno opasnih Ag.
  - Eliminišu mikroorganizme i alergene.



IgA and the intestinal microbiota: the importance of being specific, Oliver Pabst and Emma Slack, Mucosal Immunology (2020) 13:12–21; https://doi.org/10.1038/s41385-019-0227-4

Probiotici imaju ulogu u održavanju homeostaze intestinalne mikrobiote



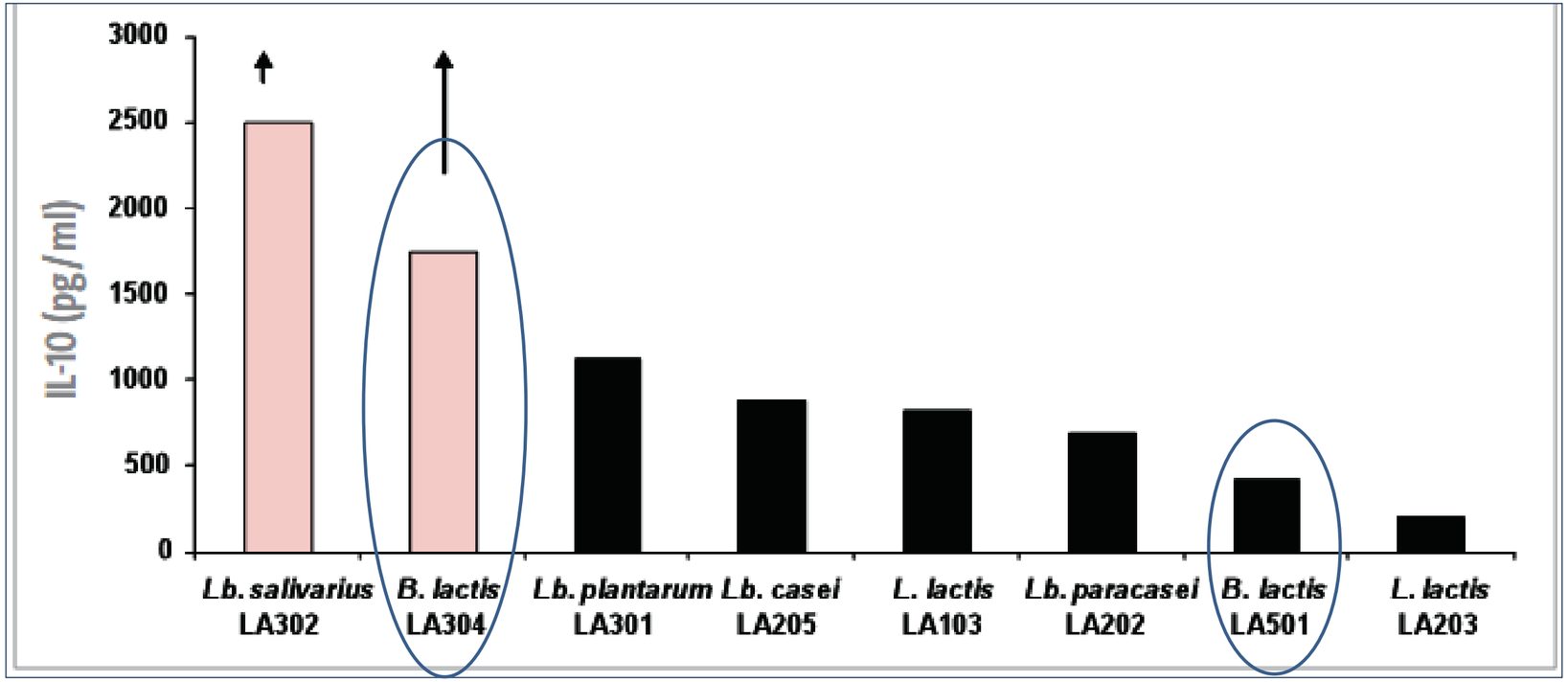
- ✓Moduliraju imunski odgovor sluznice.
- ✓Podstiču stvaranje antiinflamatornih citokina.
- ✓Olakšavaju održavanje imunološke tolerancije.

Efekti probiotka zavise od soja!

The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic
Hill, C. *et al. Nat. Rev. Gastroenterol. Hepatol.* 11, 506–514 (2014); published online 10 June 2014; doi:10.1038/nrgastro.2014.66

Izbor specifičnih sojeva je ključ imunomodulacije

Od suštinskog je značaja poznavati osobine korisnih bakterija, ali i osobine specifičnih sojeva



IL-10 koji produkuju mononuklearne ćelije iz krvi dobijene od zdravih davalaca, nakon inkubacije sa probiotskim sojevima tokom 24 sata. *INSERM, Francuska*

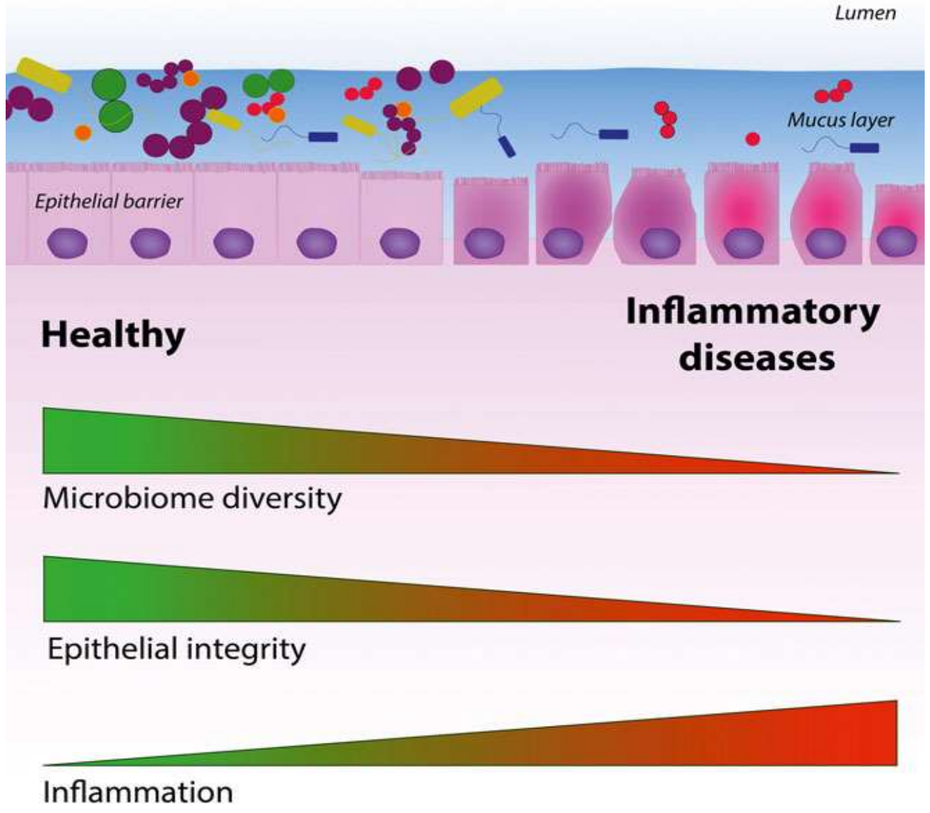
Različiti sojevi iste vrste, ***Bifidobacterium lactis***, mogu imati različita svojstva.
B. lactis LA304 stimuliše proizvodnju IL-10 **tri puta više** od ***B. lactis LA501***.

Data on file, INSERM

Imunomodulatorni efekat probiotskih sojeva *Lactobacillus salivarius* LS01 i *Bifidobacterium breve* BR03

- Sposobnost *Lactobacillus salivarius* LS01 i *Bifidobacterium breve* BR03 da regulišu smanjenje sekrecije proinflamatornih citokina kod pacijenata sa astmatmom može dovesti do poboljšanja i kontrole simptoma alregija.

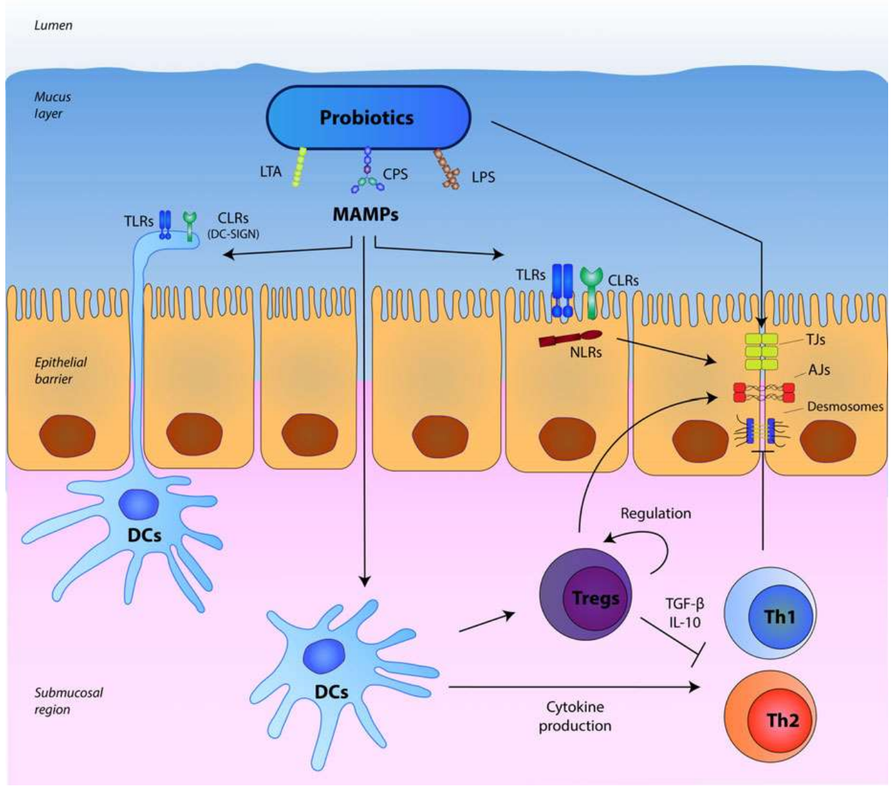
- **Zanimljivo je da u brojnim studijama kombinacija ova dva soja u istoj formulaciji nadopunjuje imunomodulatornu aktivnost svakog pojedinačnog soja.**



Drago L, De Vecchi E, Gabrieli A, De Grandi R, Toscano M. Immunomodulatory Effects of Lactobacillus salivarius LS01 and Bifidobacterium breve BR03, Alone and in Combination, on Peripheral Blood Mononuclear Cells of Allergic Asthmatics. Allergy Asthma Immunol Res. 2015 Jul;7(4):409-13. doi: 10.4168/aair.2015.7.4.409. Epub 2015 Mar 5.

Imunomodulatorni efekti *L. salivarius* i *B. breve*

- Ovi probiotski sojevi imaju sposobnost da inhibiraju lučenje proinflamatornih citokina.
- *Lactobacillus salivarius i Bifidobacterium breve* aktiviraju monocite i proizvodnju IL-10 koji inhibira proinflamatorne citokine IL-4 i IL-5.
- Ekspresija IL-10 je smanjena u makrofazima u alveolama pacijenata sa astmom.

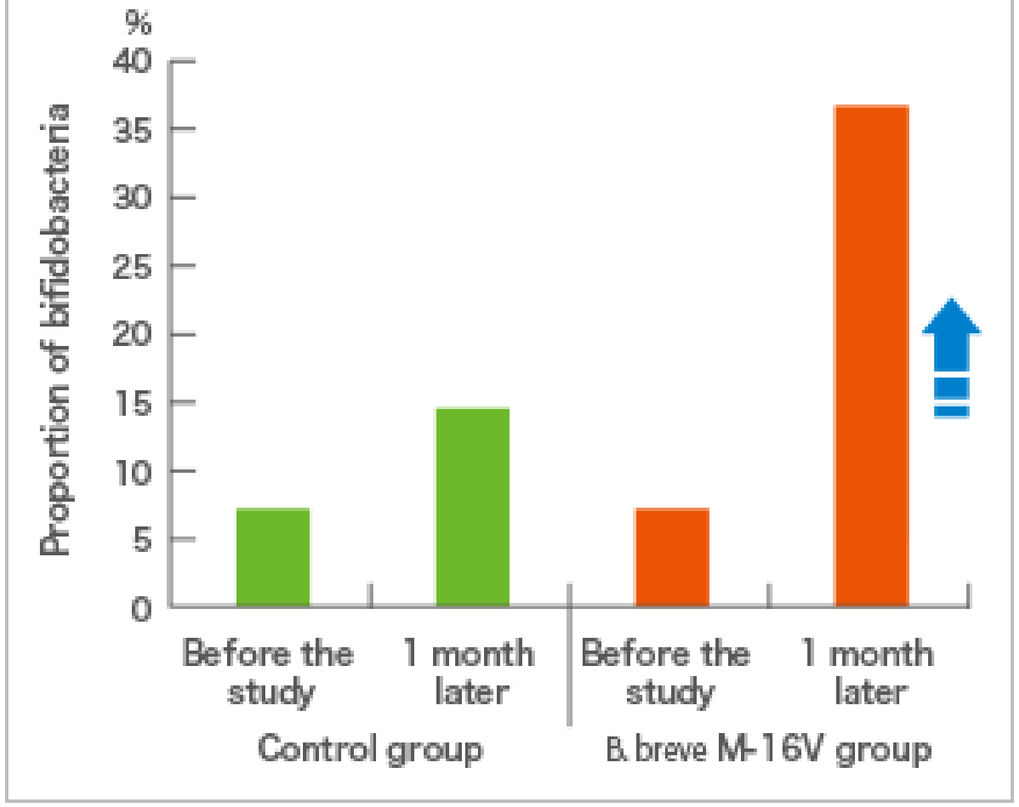


Drago L, De Vecchi E, Gabrieli A, De Grandi R, Toscano M. Immunomodulatory Effects of Lactobacillus salivarius LS01 and Bifidobacterium breve BR03, Alone and in Combination, on Peripheral Blood Mononuclear Cells of Allergic Asthmatics. Allergy Asthma Immunol Res. 2015 Jul;7(4):409-13. doi: 10.4168/aair.2015.7.4.409. Epub 2015 Mar 5.

Bifidobacterium breve M-16V - Anti-allergic effect

Proportion of bifidobacteria after *B. breve* M-16V administration

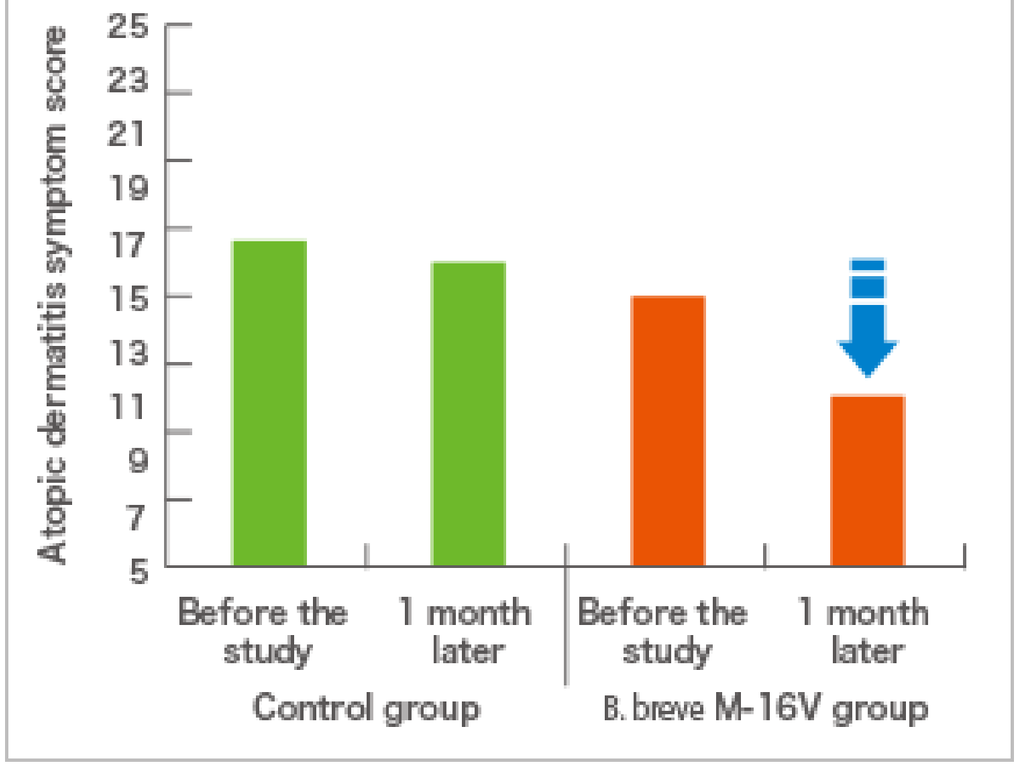
Increases the number of bifidobacteria



(Hattori K. *et al*,Japanese Journal of Allergology,2003)

Changes in atopic dermatitis symptom scores after *B. breve* M-16V administration

Relieves atopic dermatitis symptoms

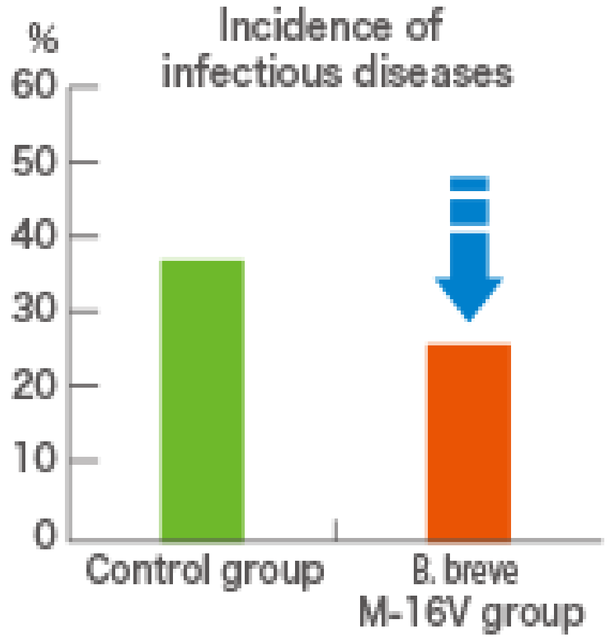


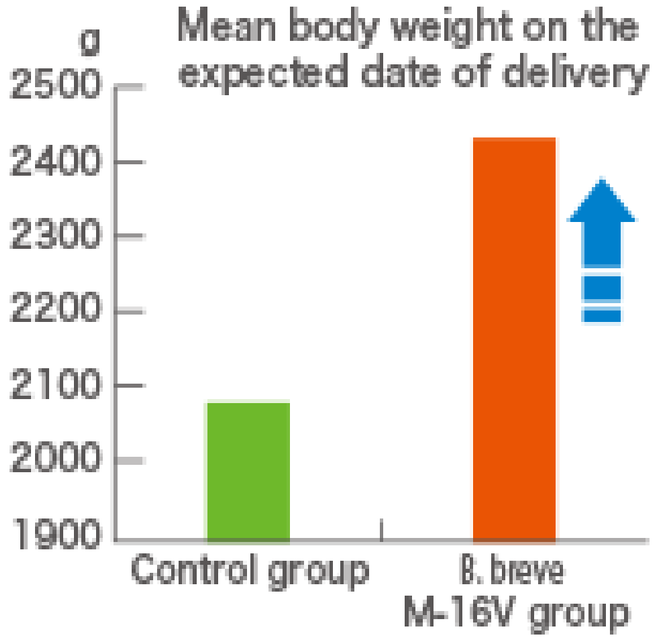
(Hattori K. *et al*,Japanese Journal of Allergology,2003)

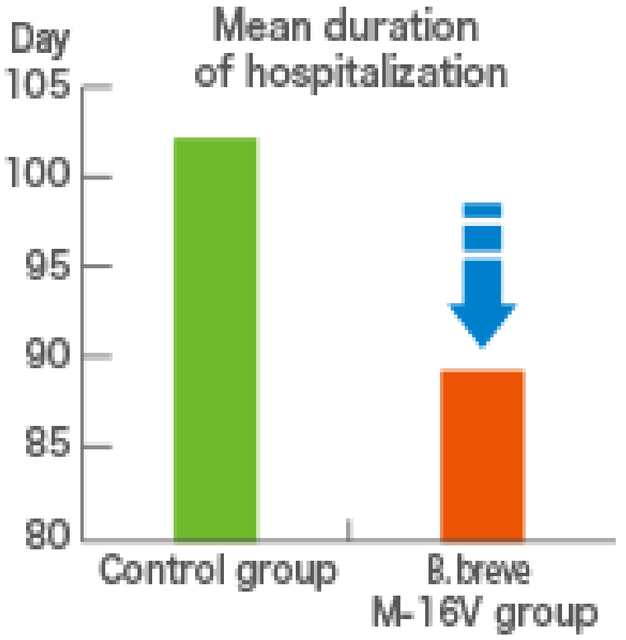
Bifidobacterium breve u prevenciji infekcija rastu beba rođenih sa malom telesnom masom

Effects of *B. breve* M-16V administration for preventing infection and promoting the growth of low birth weight infants

Promoting the growth of low birth weight infants



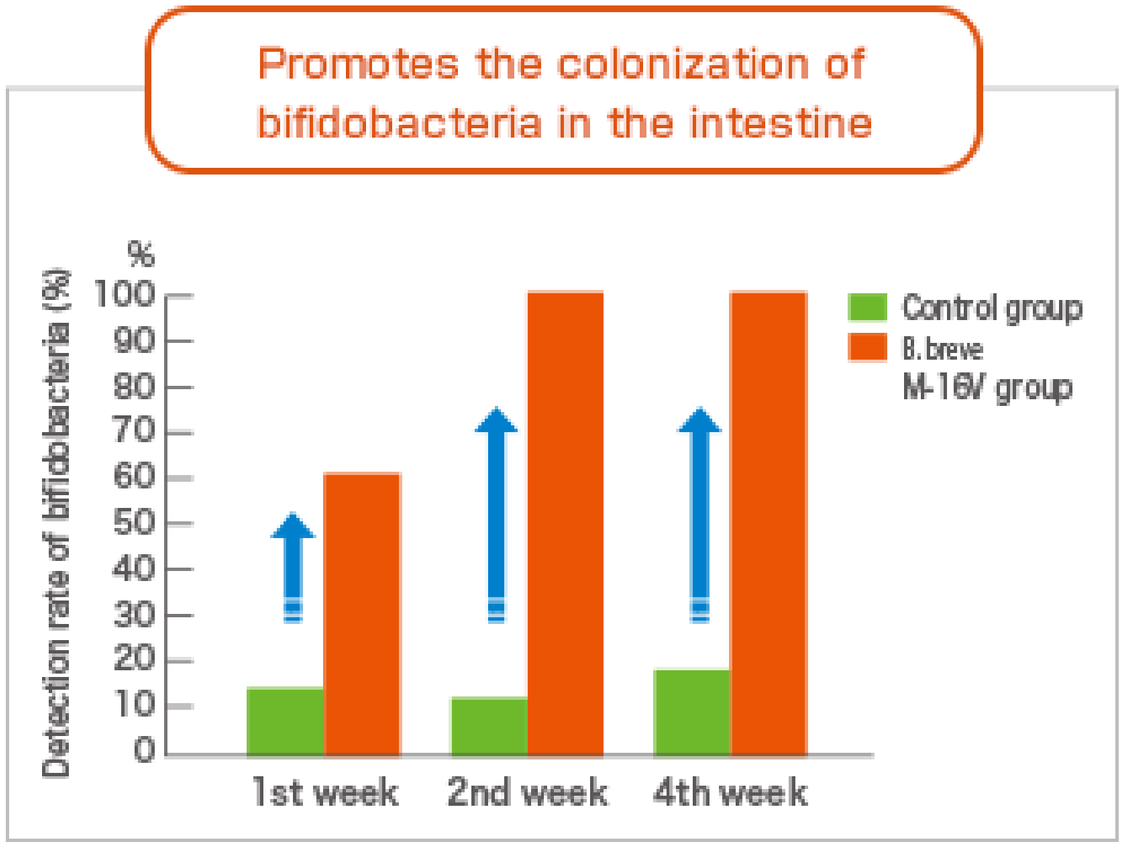




(Sato Y. *et al*,Acta Neonatologica Japonica,2003)

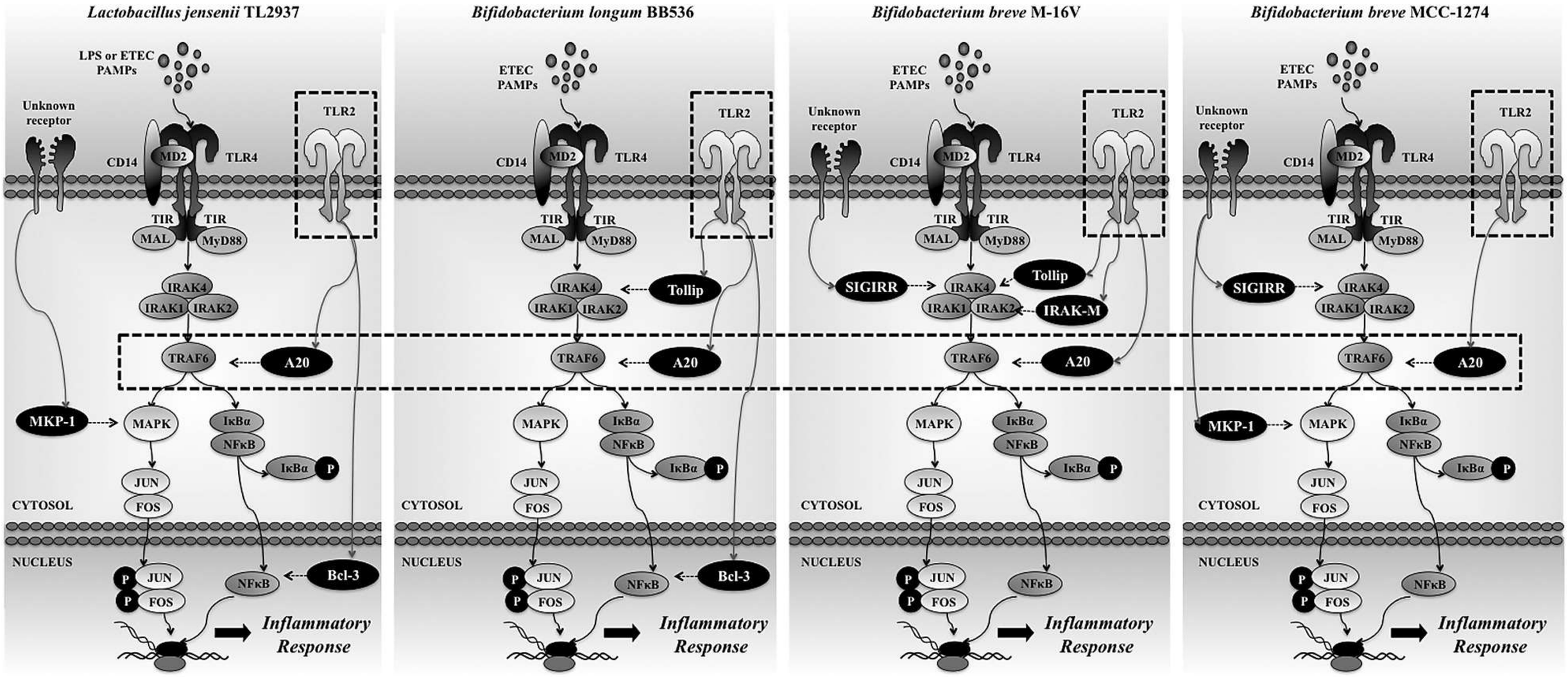
Rast beba rođenih sa malom telesnom masom sa bifodocaterium breve u stolici

Percentage of low birth weight
infants having bifidobacteria in the faces
during *B. breve* M-16V administration

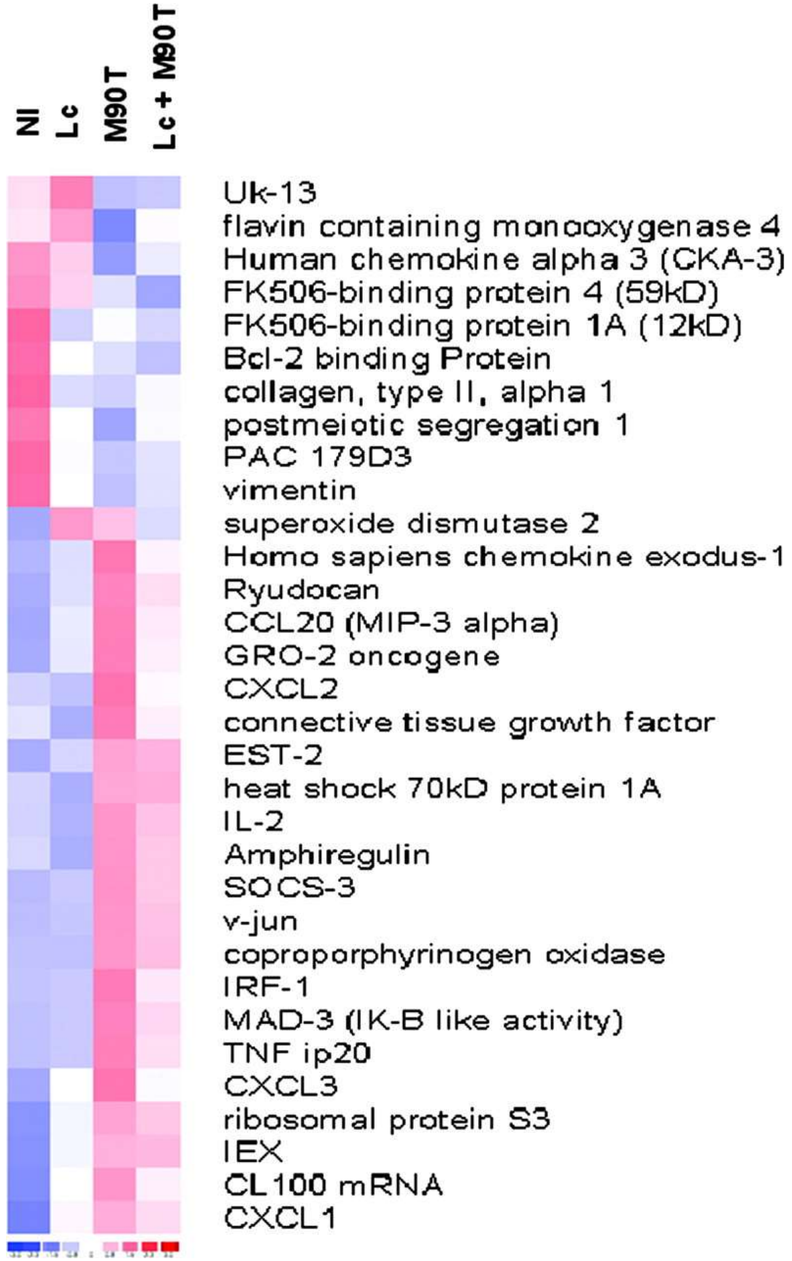


(Ishizeki S. *et al*,J Jpn Pediatr Soc,2004)

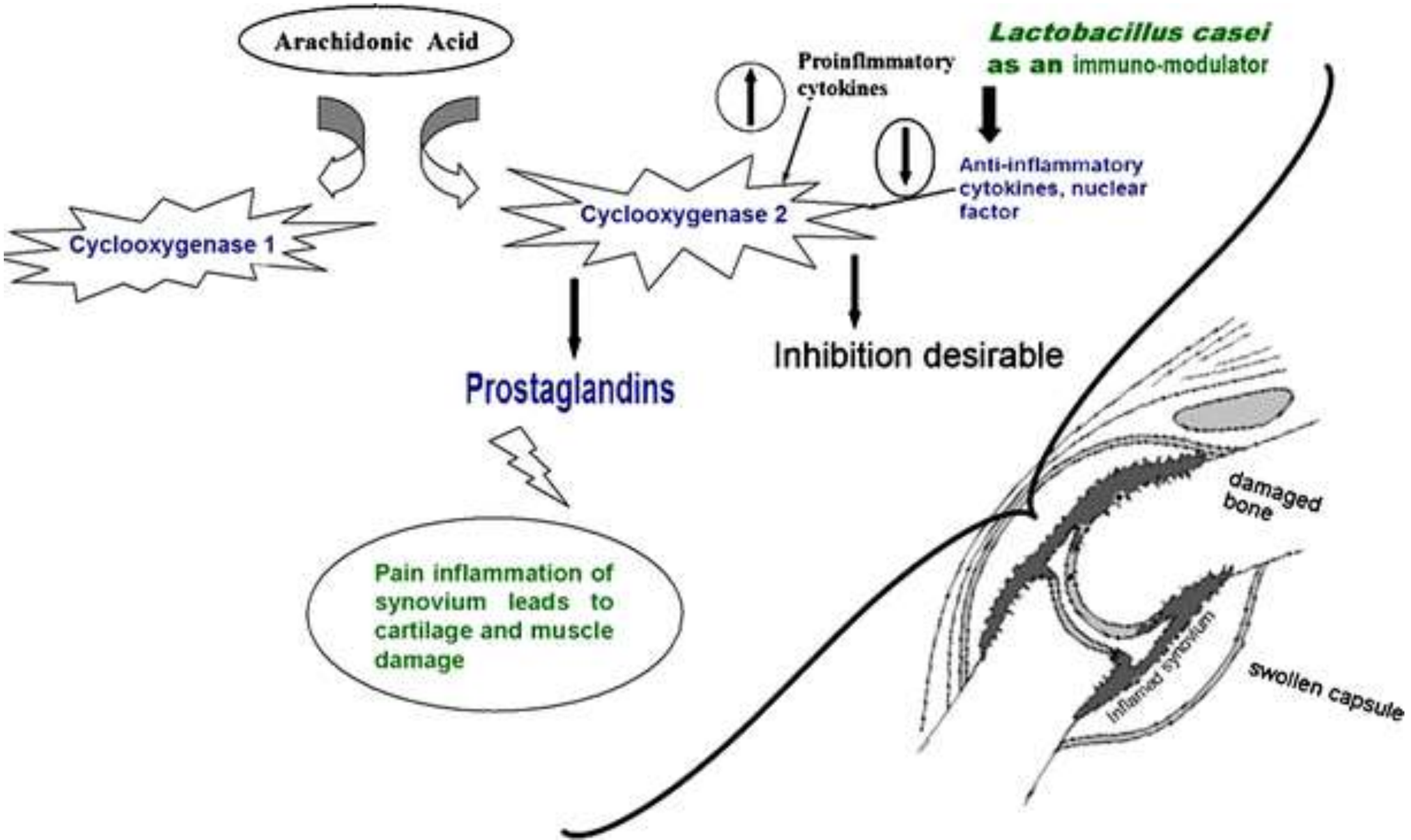
Predloženi mehanizam imunomodulacije



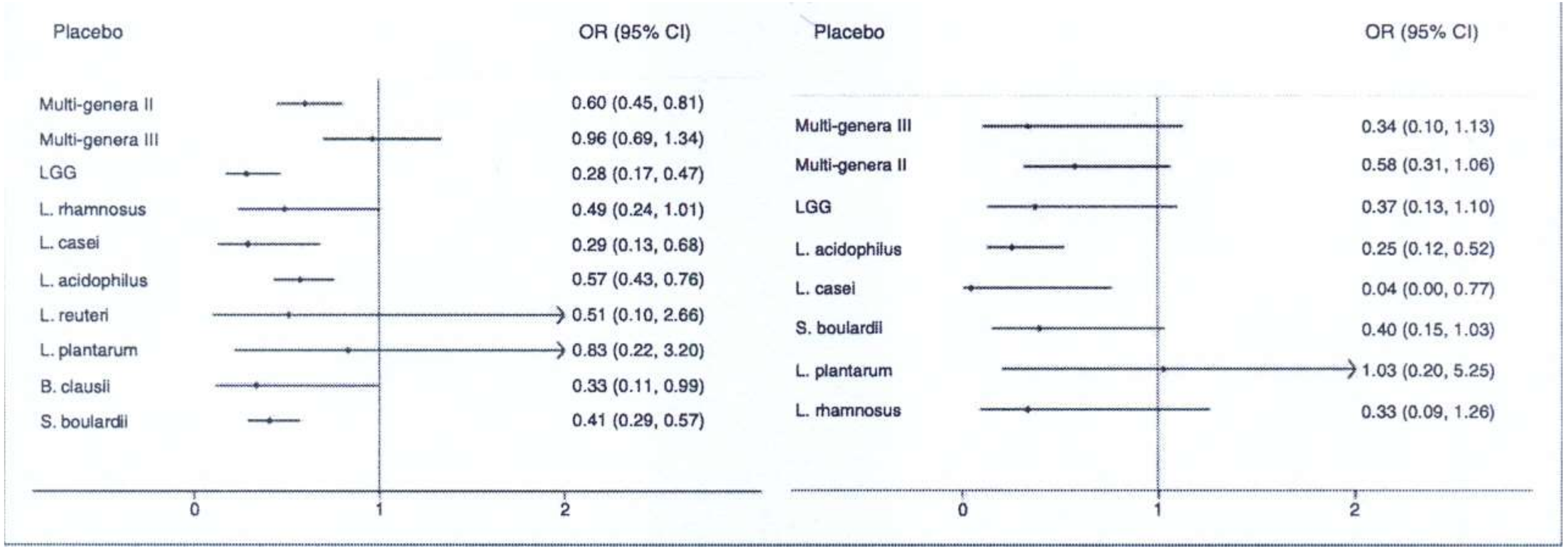
Lactobacillus casei antiinflamatorni efekat



Lactobacillus casei redukuje inflamaciju



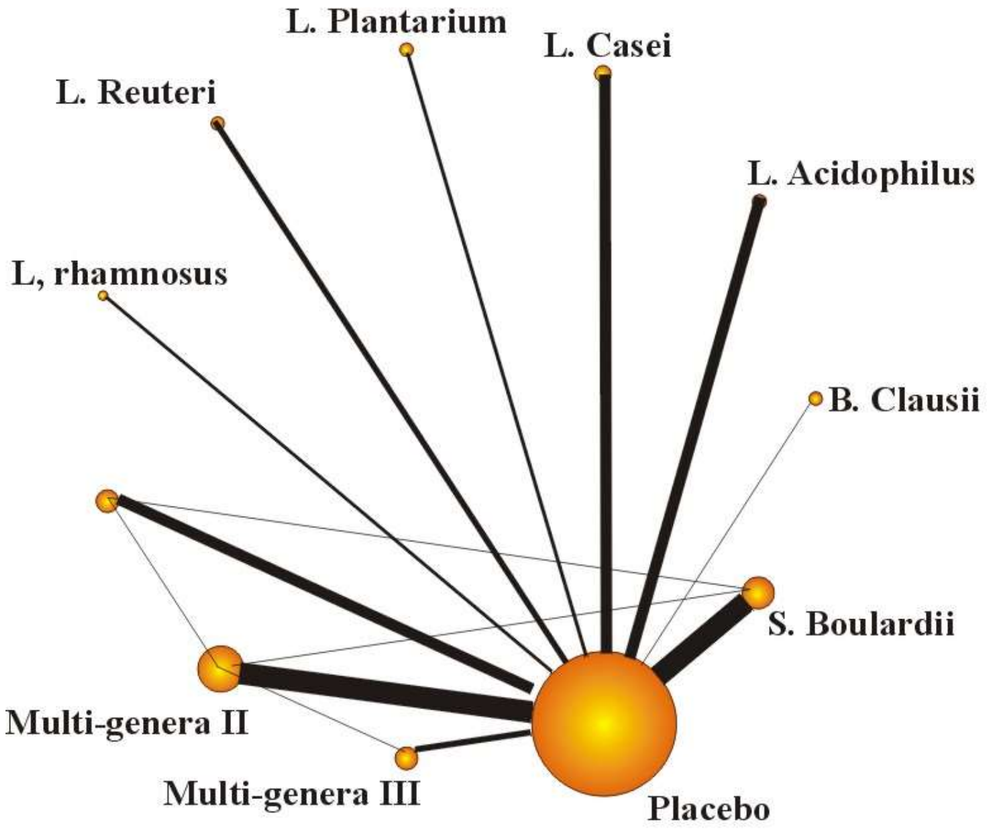
L. Casei u lečenju c. Difficile



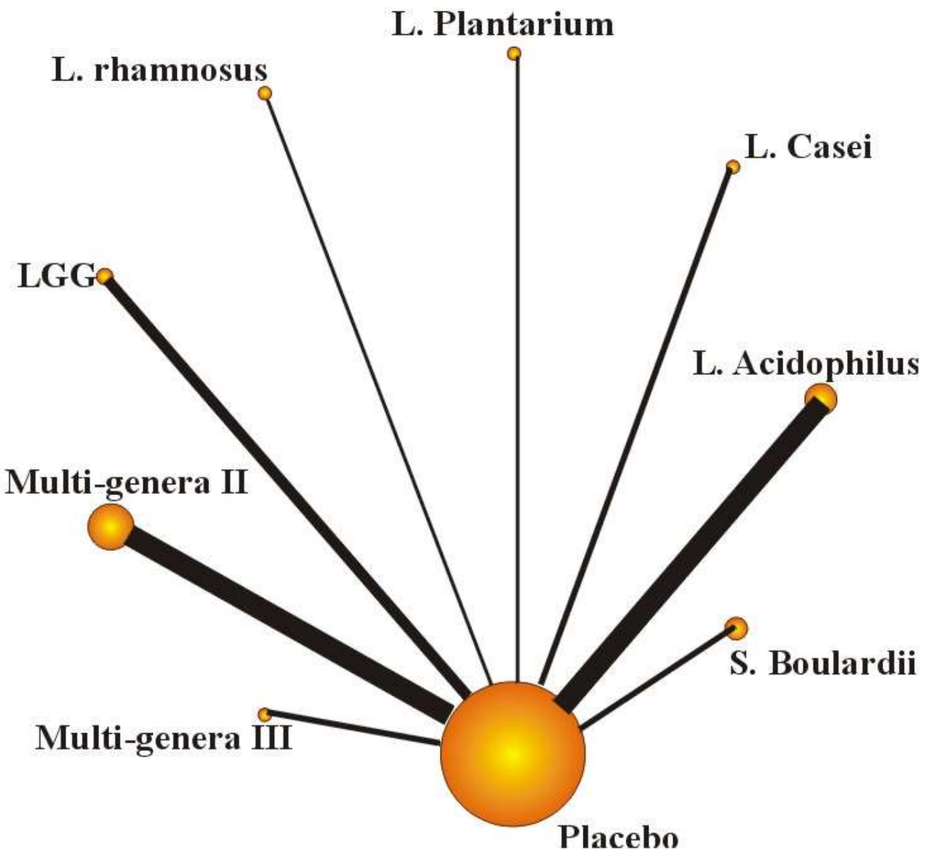
L. Casei je najefikasniji kod infekcija izazvanim C. difficile

Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis Jiayi Cai1,2, Chunyang Zhao3,4, Yajie Du1, Yaqiong Zhang1, Mingyi Zhao1 and Qingchun Zhao1,2 United European Gastroenterology Journal 2018, Vol. 6(2) 169180

Efikasnost l. Casei u lečenju diareja



Efikasnost u lečenju dijarea



Incidenca dijareja u poređanju sa placebom

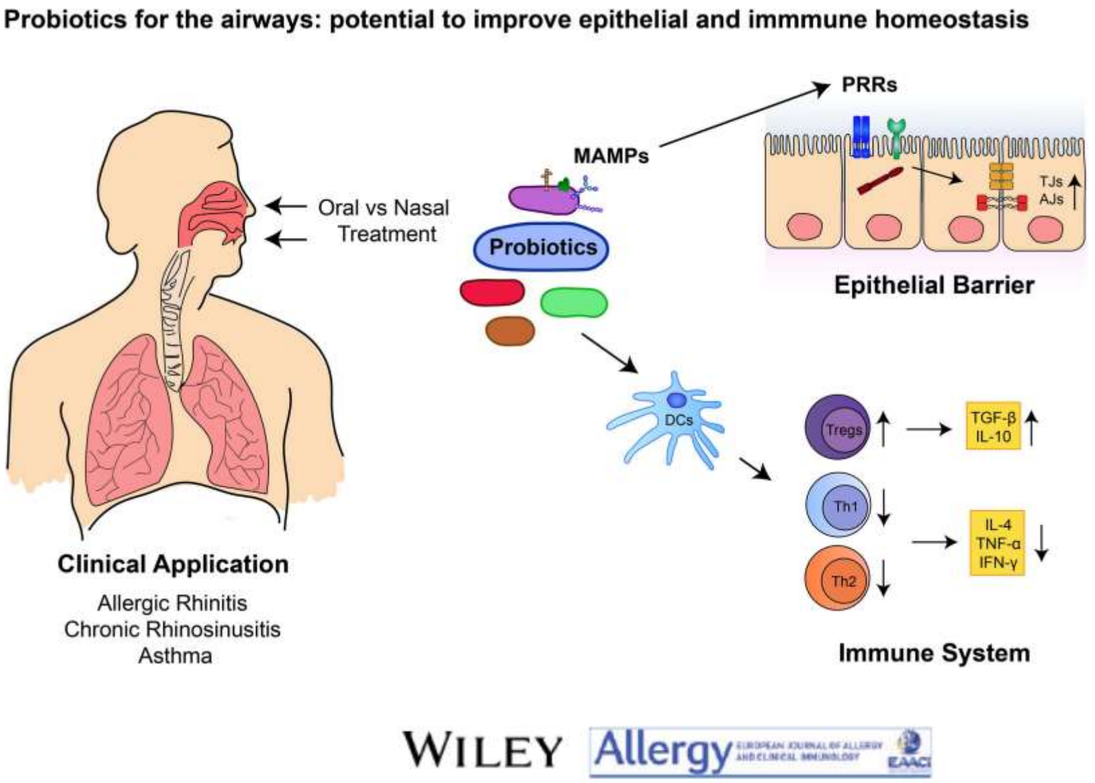
Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis Jiayi Cai1,2, Chunyang Zhao3,4, Yajie Du1, Yaqiong Zhang1, Mingyi Zhao1 and Qingchun Zhao1,2 United European Gastroenterology Journal 2018, Vol. 6(2) 169180

Probiotici, alergijski rinitis i astma

Disbioza kod hroničnih bolesti disajnih puteva izgleda da se javlja istovremeno sa poremećajima epitelne barijere, to je primećeno kod alergijske astme, alergijskog rinitisa i hroničnog rinosinuzitisa.

Klinički potencijal probiotika:

- Obnavljaju oštećenu epitelijalnu barijeru.
- Moduliraju imunski odgovor domaćina interakcijom sa dendritičkim ćelijama (DC).
- Promovišu regulatorne T ćelije (T-reg) i smanjuju T helper 1 (Th1) i T helper 2 (Th2) ćelije



WILEY Allergy

Martens K, Pugin B, De Boeck I, et al. Probiotics for the airways: Potential to improve epithelial and immune homeostasis. Allergy. 2018;73:1954–1963. https://doi.org/10.1111/all.13495

Vitamin D i respiratorne infekcije

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

Adrian R Martineau,1,2 David A Jolliffe,1 Richard L Hooper,1 Lauren Greenberg,1 John F Aloia,3 Peter Bergman,4 Gal Dubnov-Raz,5 Susanna Esposito,6 Davaasambuu Ganmaa,7 Adit A Ginde,8 Emma C Goodall,9 Cameron C Grant,10 Christopher J Griffiths,1,2,11 Wim Janssens,12 Ilkka Laaksi,13 Semira Manaseki-Holland,14 David Mauger,15 David R Murdoch,16 Rachel Neale,17 Judy R Rees,18 Steve Simpson,Jr19 Iwona Stelmach,20 Geeta Trilok Kumar,21 Mitsuyoshi Urashima,22 Carlos A Camargo Jr

Objectives
assess effect of vitamin D supplementation on risk of ARI
Design
Systematic review and meta-analysis of 25 eligible of RTC (total 11 321 participants)
Results
Vitamin D supplementation reduced the risk of ARI
Adjustued odds ratio 0.88 (0.81 – 0.96) 96% CI

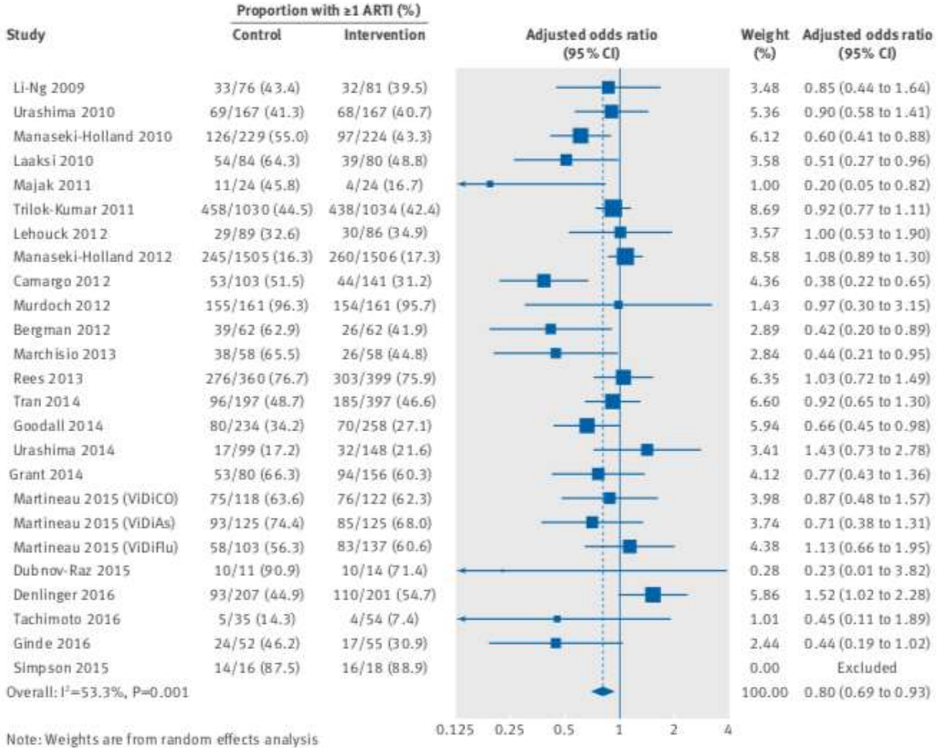
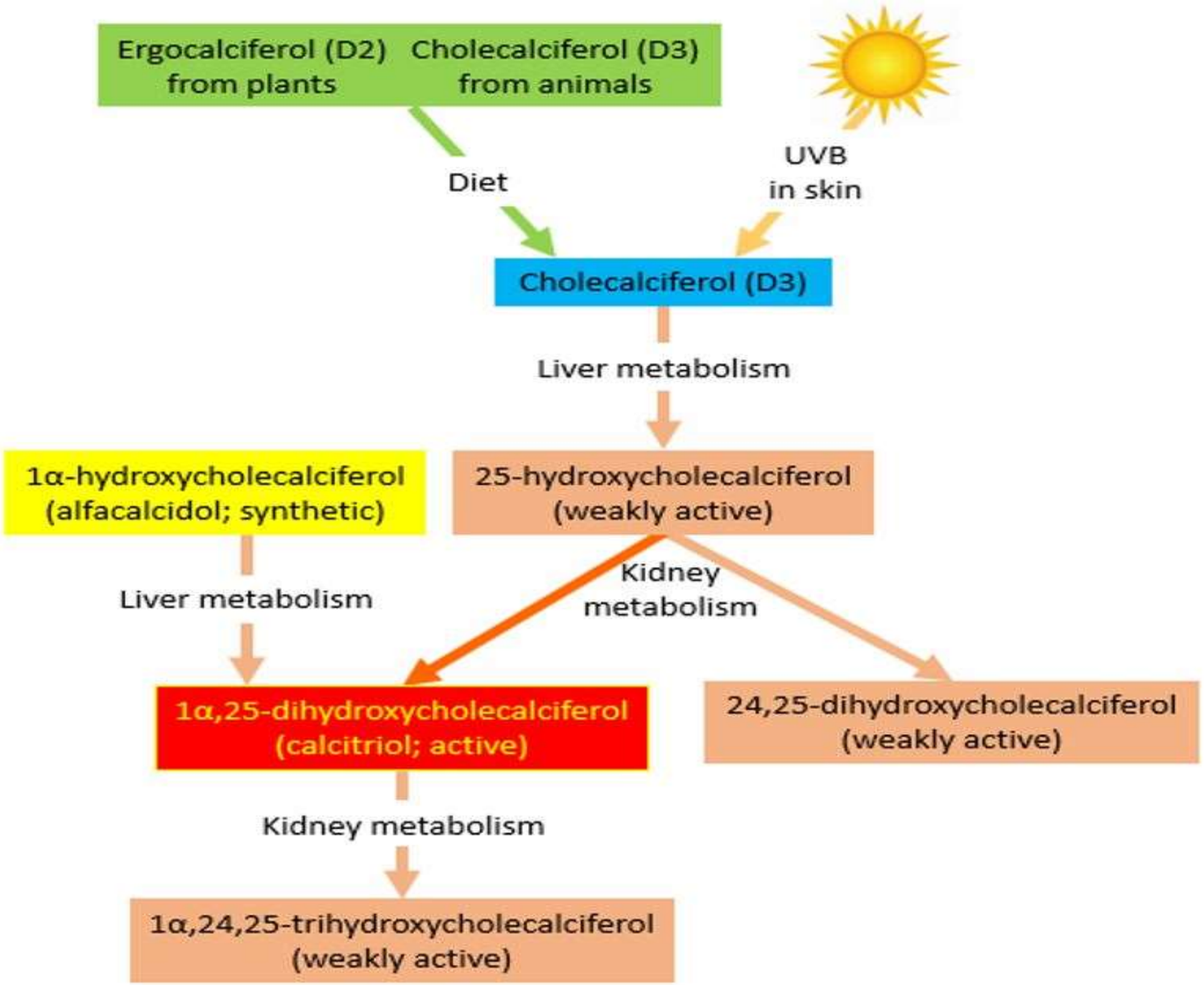


Fig 2 | Two step individual participant data meta-analysis: proportion of participants experiencing at least one acute respiratory tract infection (ARTI). Data from trial by Simpson et al were not included in this two step meta-analysis, as an estimate for the effect of the intervention in the study could not be obtained in the regression model owing to small sample size

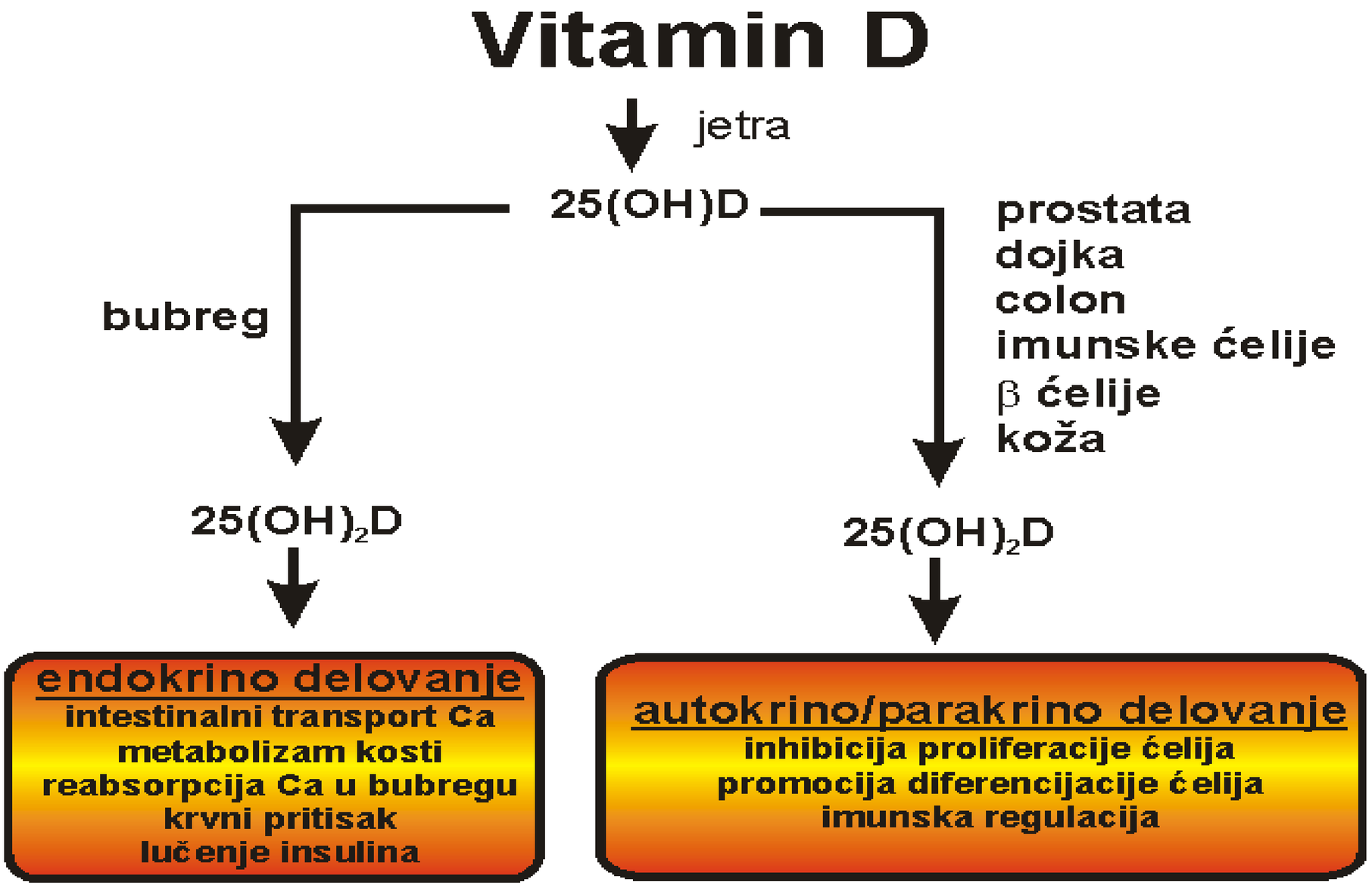
25 randomizovanih kliničkih studija
Ukupno 11 321 učesnik
Suplementacija vitaminom D smanjuje rizik od akutnih respiratornih infekcija

Martineau et al., BMJ 2017;356:i6583 | doi: 10.1136/bmj.i6583

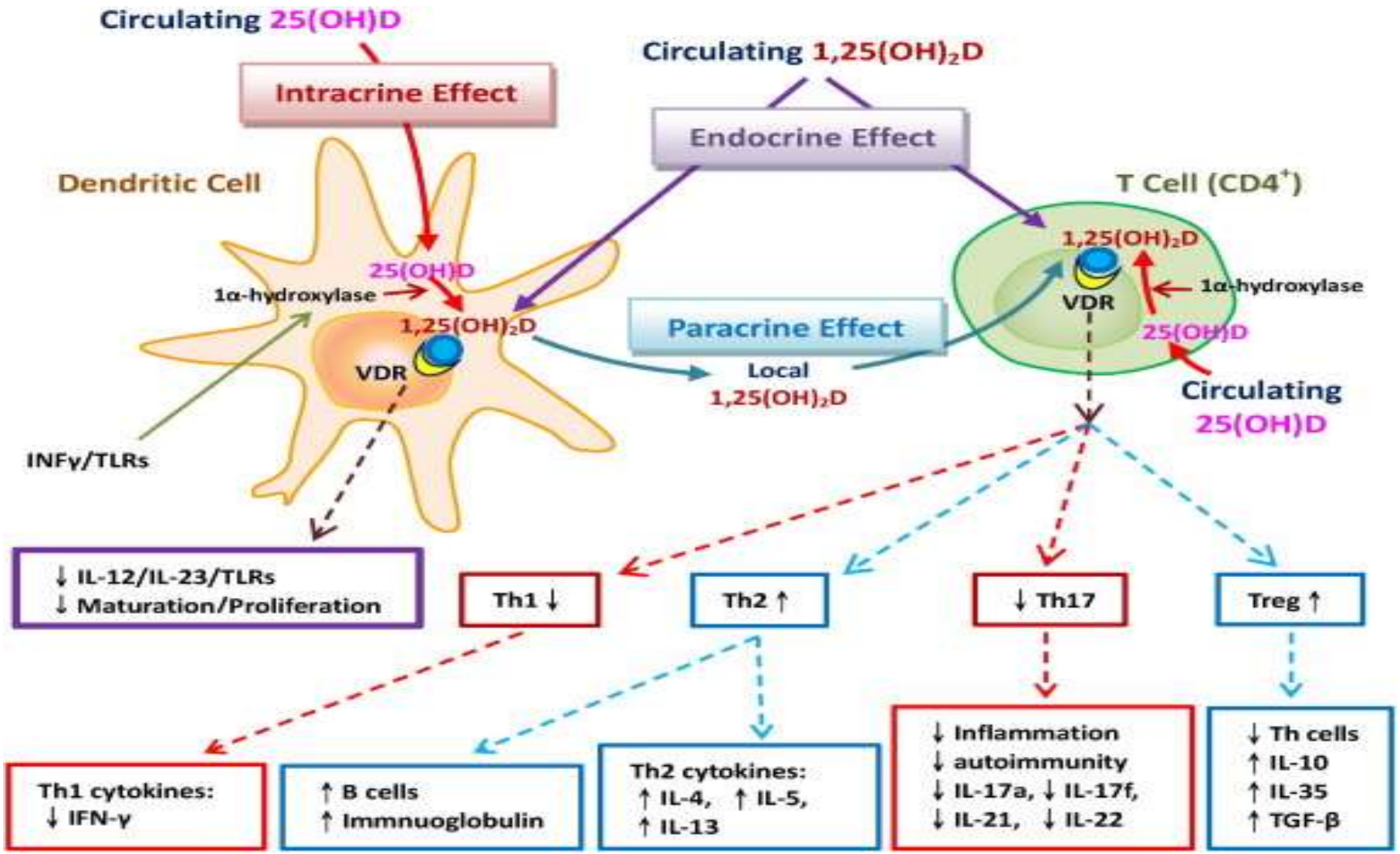
Metabolizam vitamina D



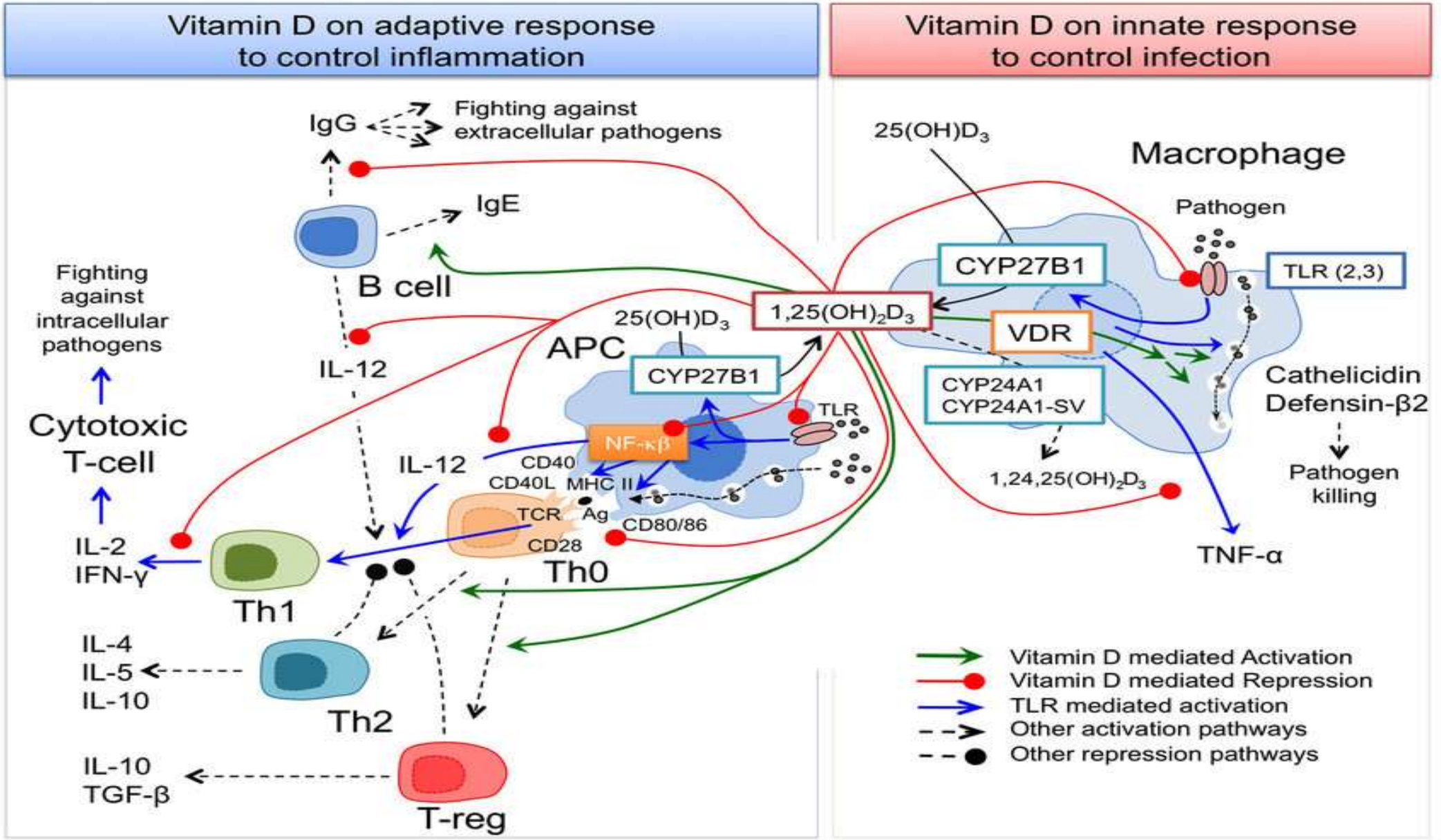
Mehanizam delovanja vitamina D



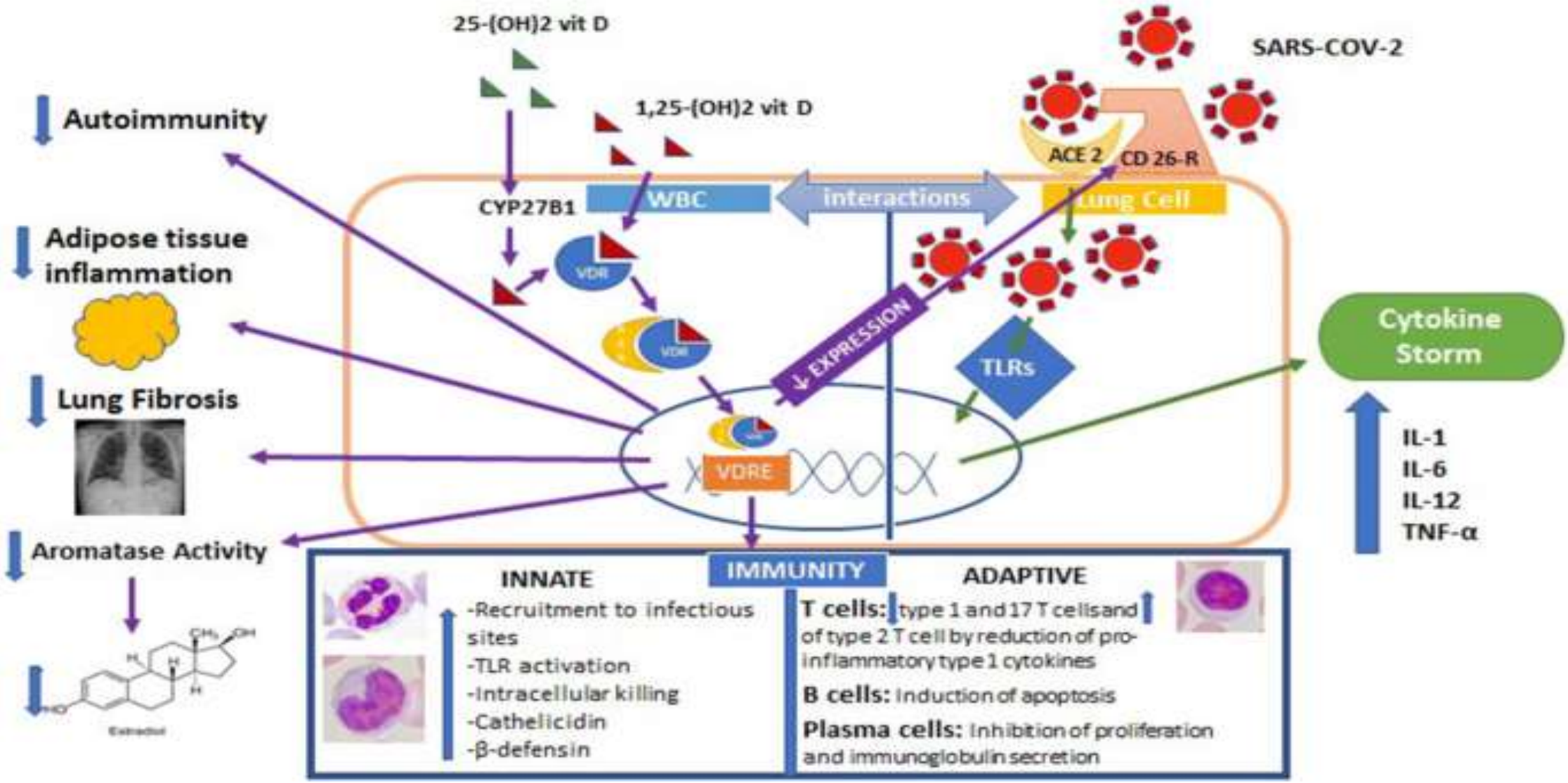
Vitamin D i imunoregulacija



Dejstvo vitamina D na urođeni i stečeni odgovor imunog sistema

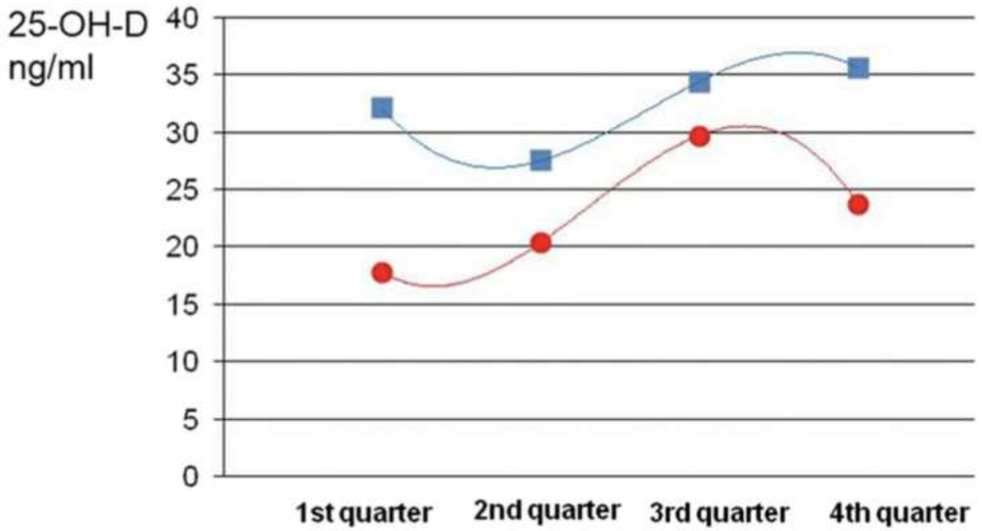


Moguća uloga vitamina D kod covid-19 infekcije kod dece



Vitamin D3 i suplementacija kod dece – DINOS studija

- Odgovarajuća doza suplementacije vitamina D3 kod dece je još uvek predmet ispitivanja.
- Preporučena doza od 600–1000 IU vitamina D3/dan nije dovoljna da bi se dostigao nivo u serumu od najmanje 30 ng/ml (75 nmol/l) kod dece na severu Italije tokom > 12 meseci.
- Cilj ove studije je bio da se analizira efekat sezonske suplementacije sa **1500 IU (=37,5 µg) vitamina D3/dan**.

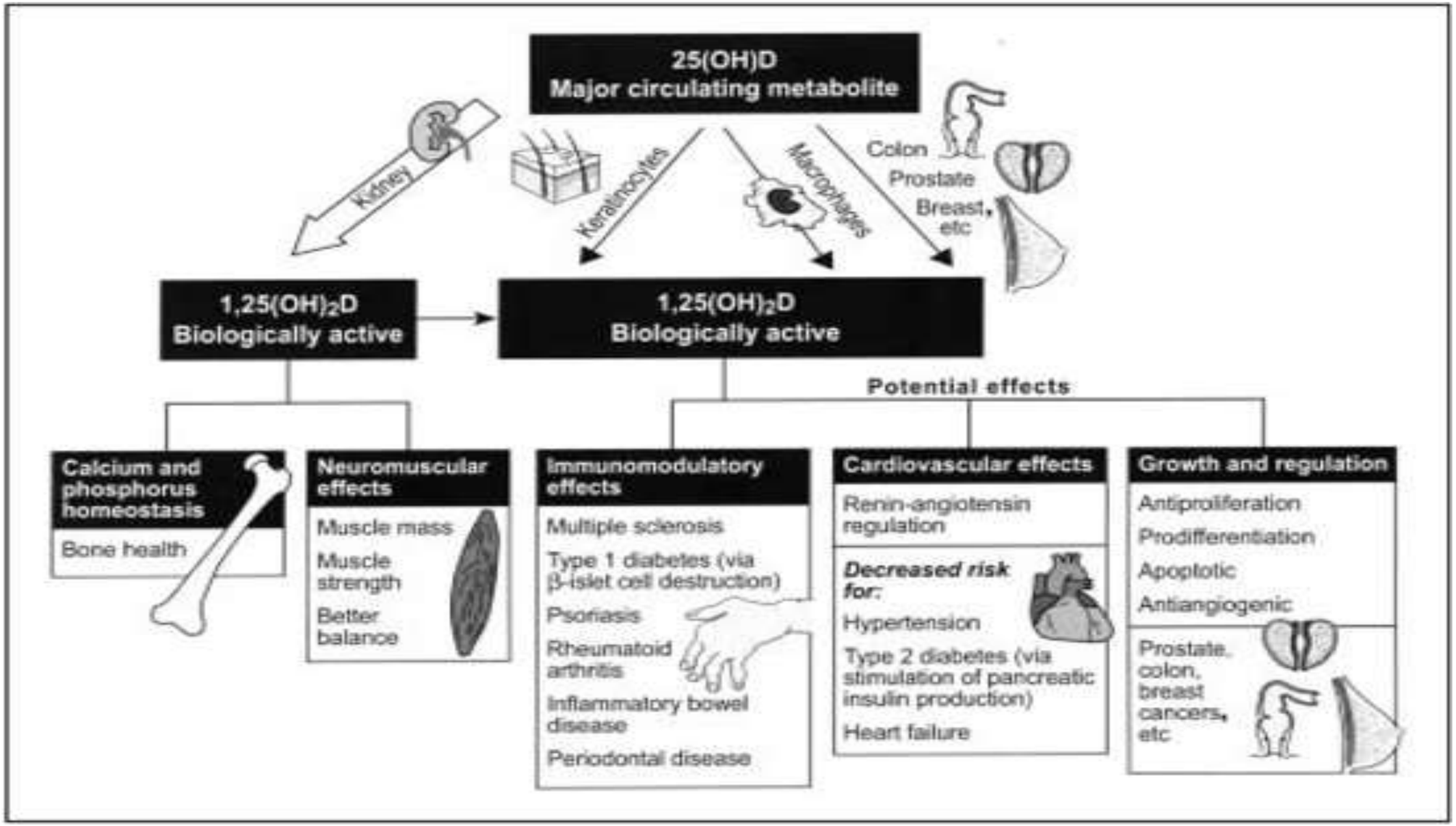


Sever Italije i Beograd su skoro na istoj 45toj paraleli

ZAKLJUČAK: Suplementacija vitaminom D sa najmanje **1500 IU vitamina D3/dan** od novembra do aprila pronađena je prikladna za decu u severnoj Italiji. Produženje suplementacije do maja bi moglo biti korisno[1].

1. Mazzoleni, S., Magni, G. & Toderini, D. Effect of vitamin D3 seasonal supplementation with 1500 IU/day in north Italian children (DINOS study). *Ital J Pediatr* **45,** 18 (2019). https://doi.org/10.1186/s13052-018-0590-x
2. Saggese G, Vierucci F, Prodam F, et al. Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians. *Ital J Pediatr*. 2018;44(1):51. Published 2018 May 8. doi:10.1186/s13052-018-0488-7

Dejstva Vitamina D



Incidenca bolesti u odnosu na nivo Vitamina D u serumu

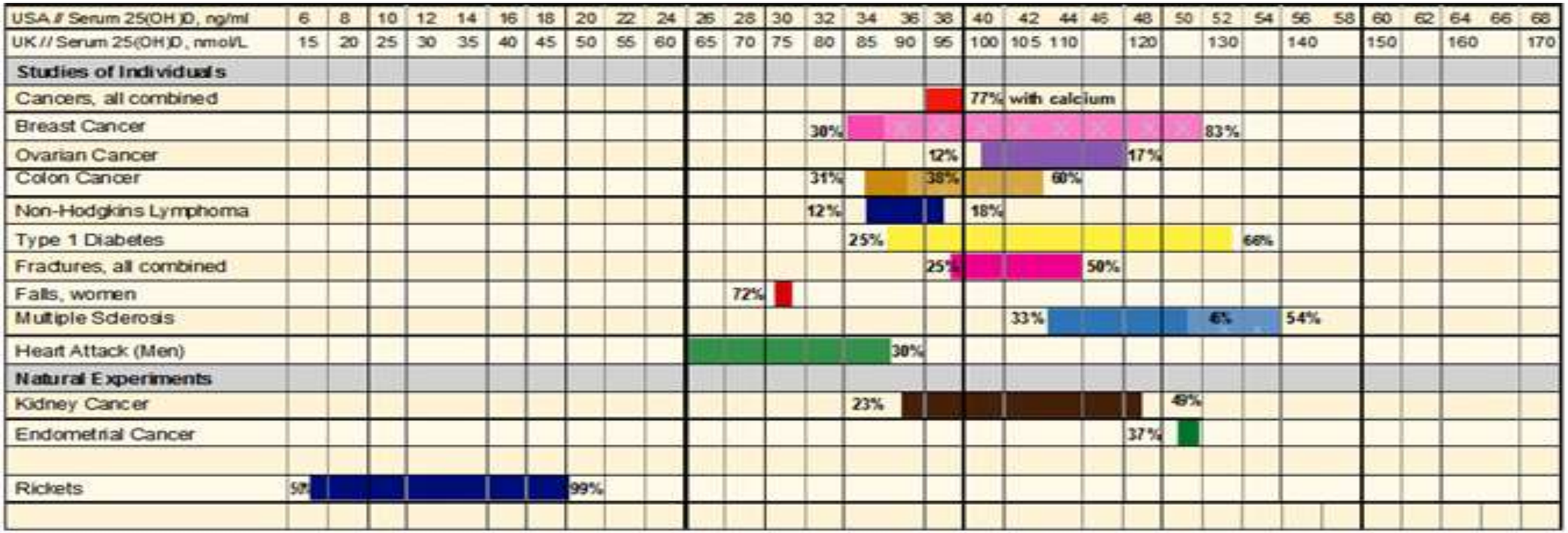
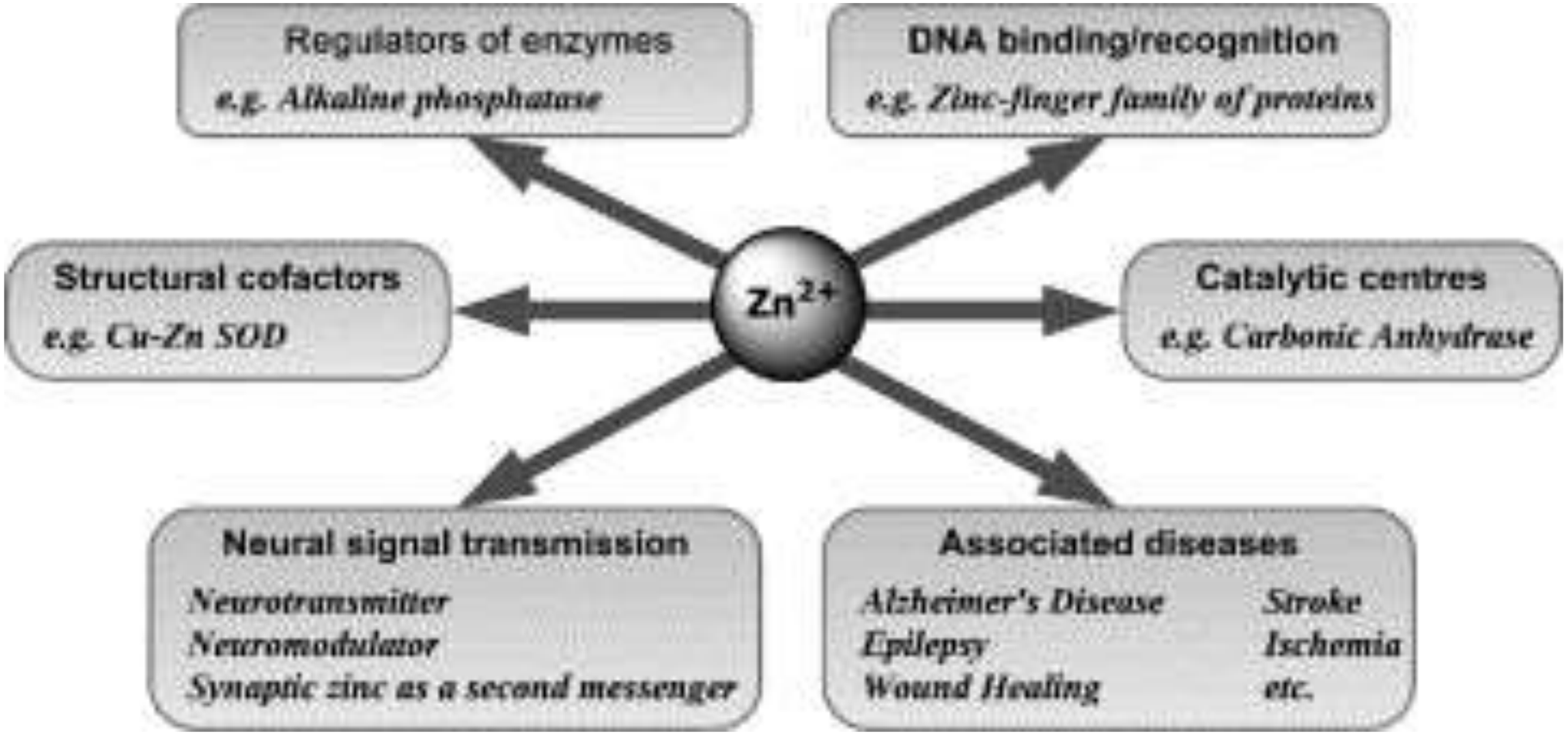
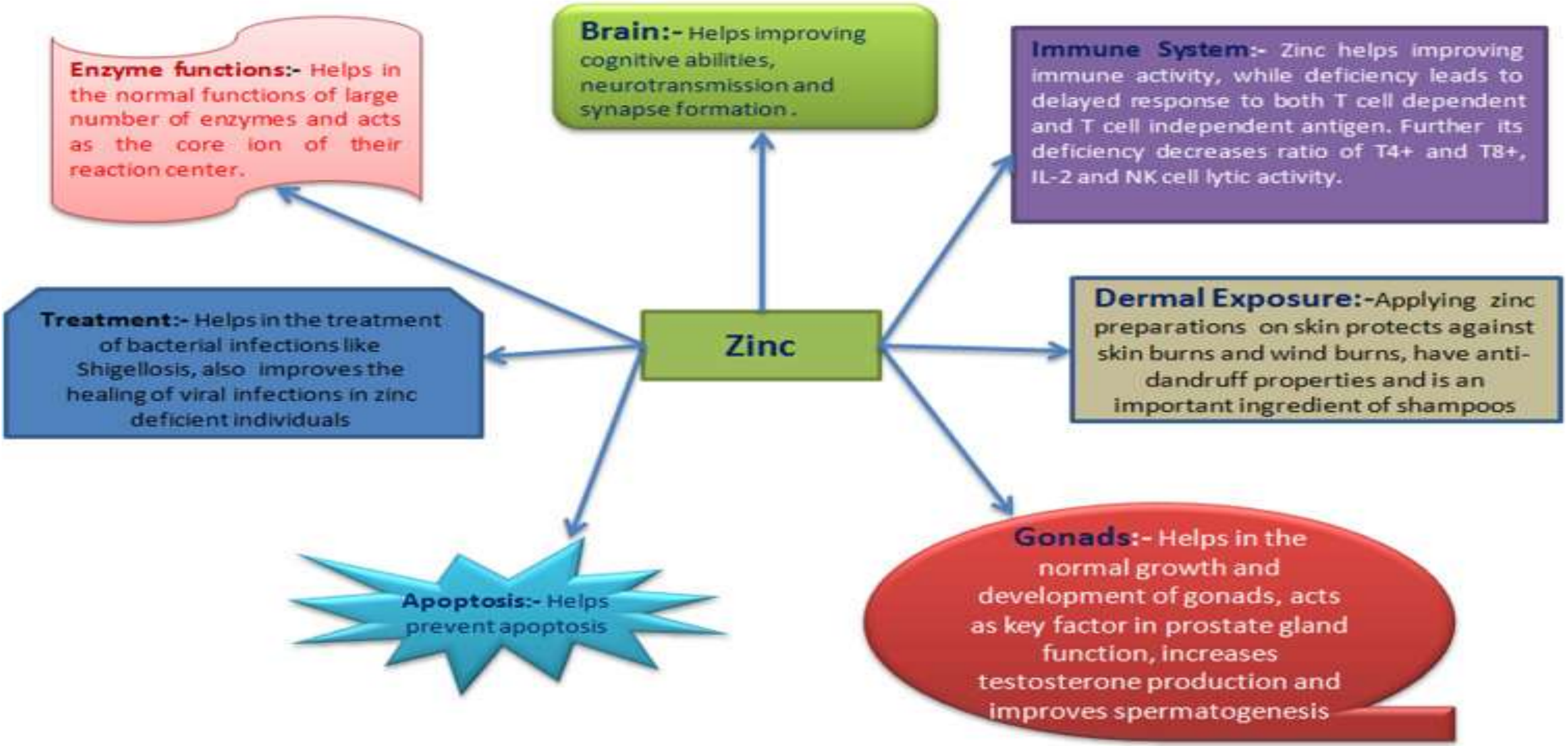


Chart prepared by: Garland CF, Baggerly CA

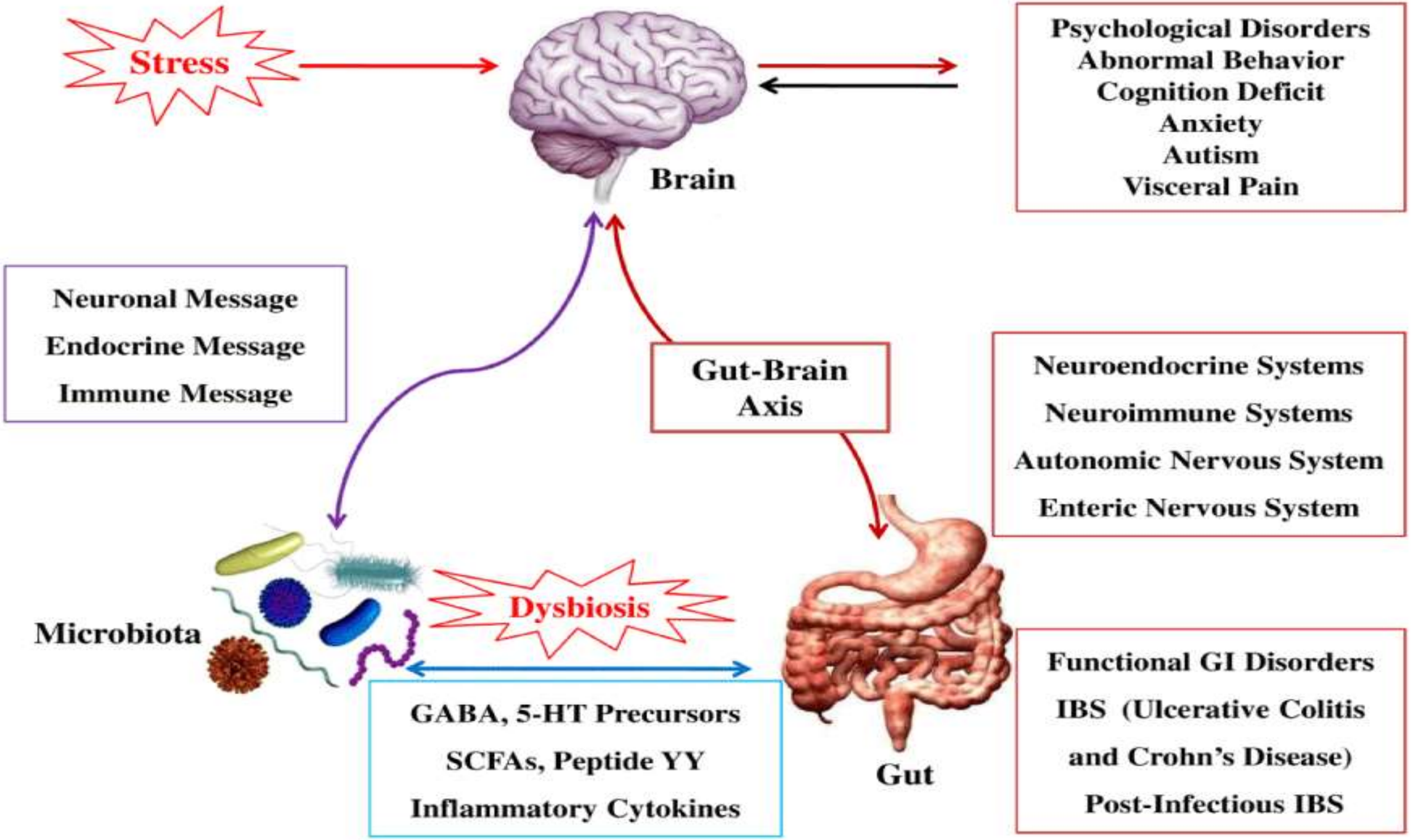
Mehanizmi delovanja cinka



Delovanje cinka na različite organe i tkiva



Stres, mikrobiota, cink i vitamin D



Sinergistički efekat za maksimalnu efikasnost

- Kombinovana primena **probiotika i vitamina D3** predstavlja novi pristup u podršci lečenja hroničnih bolesti[1].

- Brojne studije ukazuju na kliničku korist primene vitamina D3 kod hroničnih inflamatornih stanja, kao i korist primene vitamina D3, cinka i probiotika u prevenciji infekcija.[2]

- **Zajednička primena vitamina D3 i probiotika** u odnosu na placebo, **pokazuje bolje rezultate** u poređenju sa samostalnom primenom probiotika ili vitamina D3.

- Efekat je dozno zavisan[1].

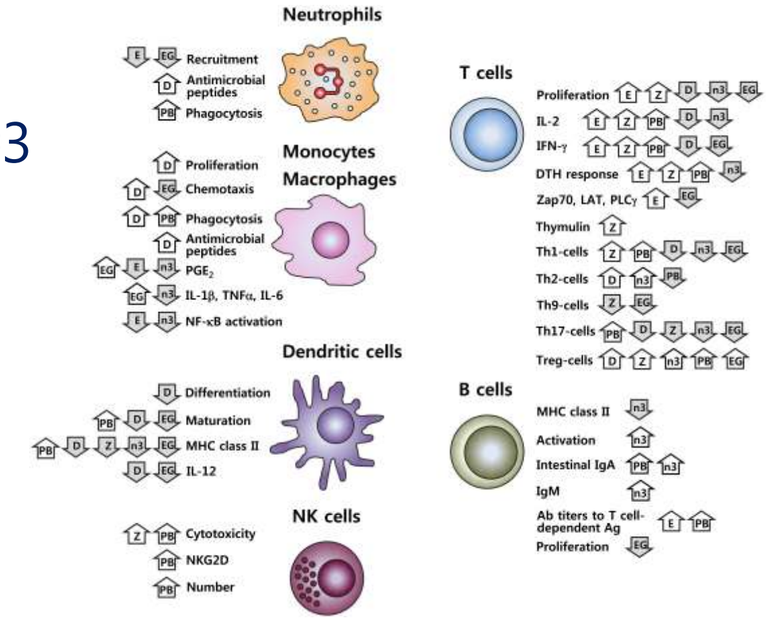


FIGURE 1 | Immune cell functions affected by vitamins D and E, zinc, n-3 PUFA, probiotics, and EGCG.

1.The Health Effects of Vitamin D and Probiotic Co-Supplementation: A Systematic Review of Randomized Controlled Trials Myriam Abboud 1,* Nutrients 2021, 13, 111. https://doi.org/10.3390/nu13010111

2.Nutritional Modulation of Immune Function: Analysis of Evidence, Mechanisms, and Clinical Relevance Dayong Wu1 *

Sinergistički efekat za maksimalnu efikasnost

- Studije pokazuju da **cink i vitamin D3** pokazuju sinergističku aktivnost u različitim fazama imunske odbrane, kao što su:
    1. Održavanje integriteta sluznica
    2. Funkcionalnost imunskih ćelija odgovornih za urođeni i adaptivni imunski odgovor.

- Nedostatak ovih nutrijenata može dovesti do oštećenja epitelnih ćelija sluznice, što ih čini podložnijim za prolazak patogena.

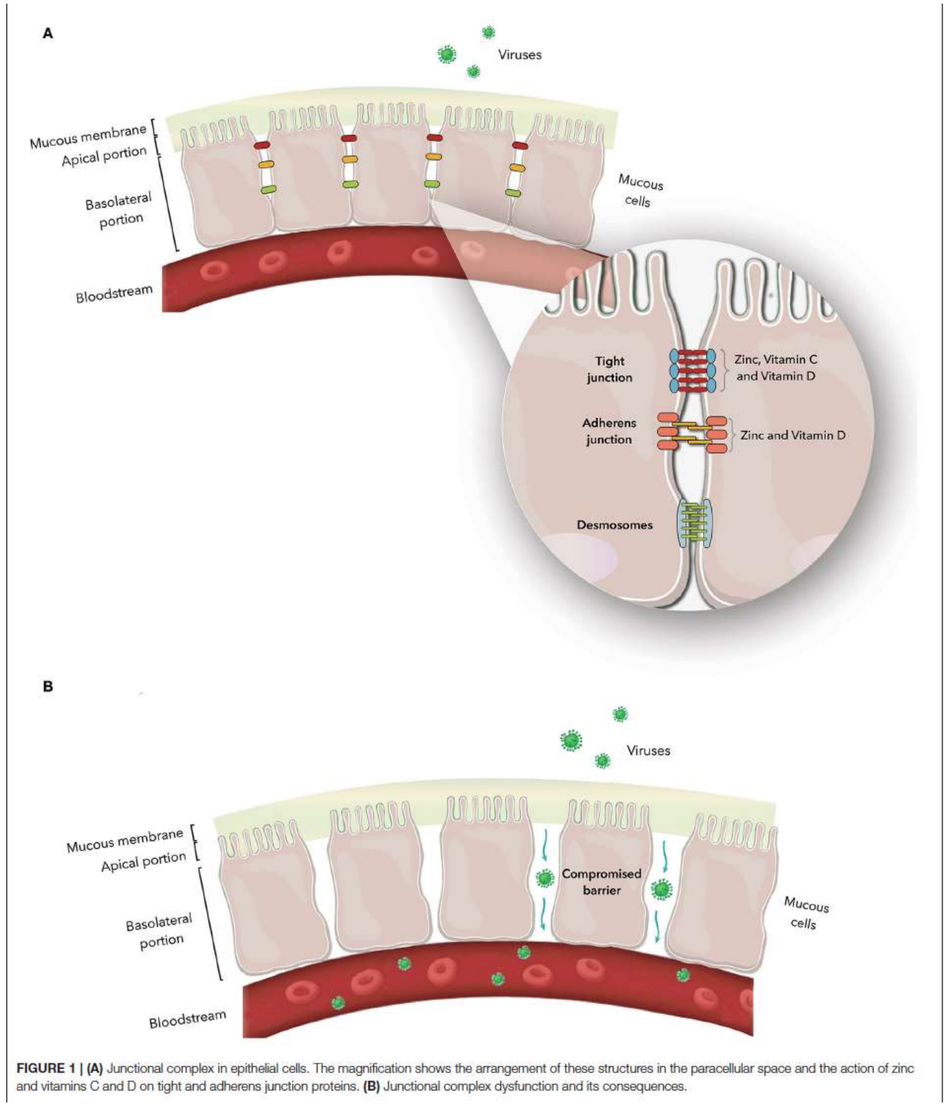


FIGURE 1 | (A) Junctional complex in epithelial cells. The magnification shows the arrangement of these structures in the paracellular space and the action of zinc and vitamins C and D on tight and adherens junction proteins. **(B)** Junctional complex dysfunction and its consequences.

Zinc, Vitamin D and Vitamin C: Perspectives for COVID-19 With a Focus on Physical Tissue Barrier Integrity José João Name1 et al.*

Zaključak

Probiotske bakterije deluju sinergistički sa vitaminom D i cinkom koriguju disbiozu i obezbedjuju normalnu reakciju imunskog sistema,omogućavajući odbranu od infektivnih patogena istovremeno umanjujući alergijske reakcije.