Probiotici e Immunomodulazione

Vito Leonardo Miniello

Unità Operativa di Nutrizione

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

microbiota

Oral cavity

Stomach and distal esophagus

Large intestine

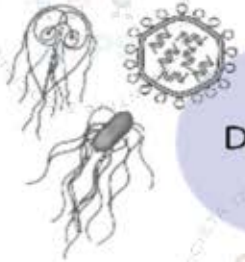
Lung and respiratory tract

Skin

Vagina

The collection of bacteria, archaea, viruses, fungi, and eukarya

microbiota intestinale



Defense

Immune function

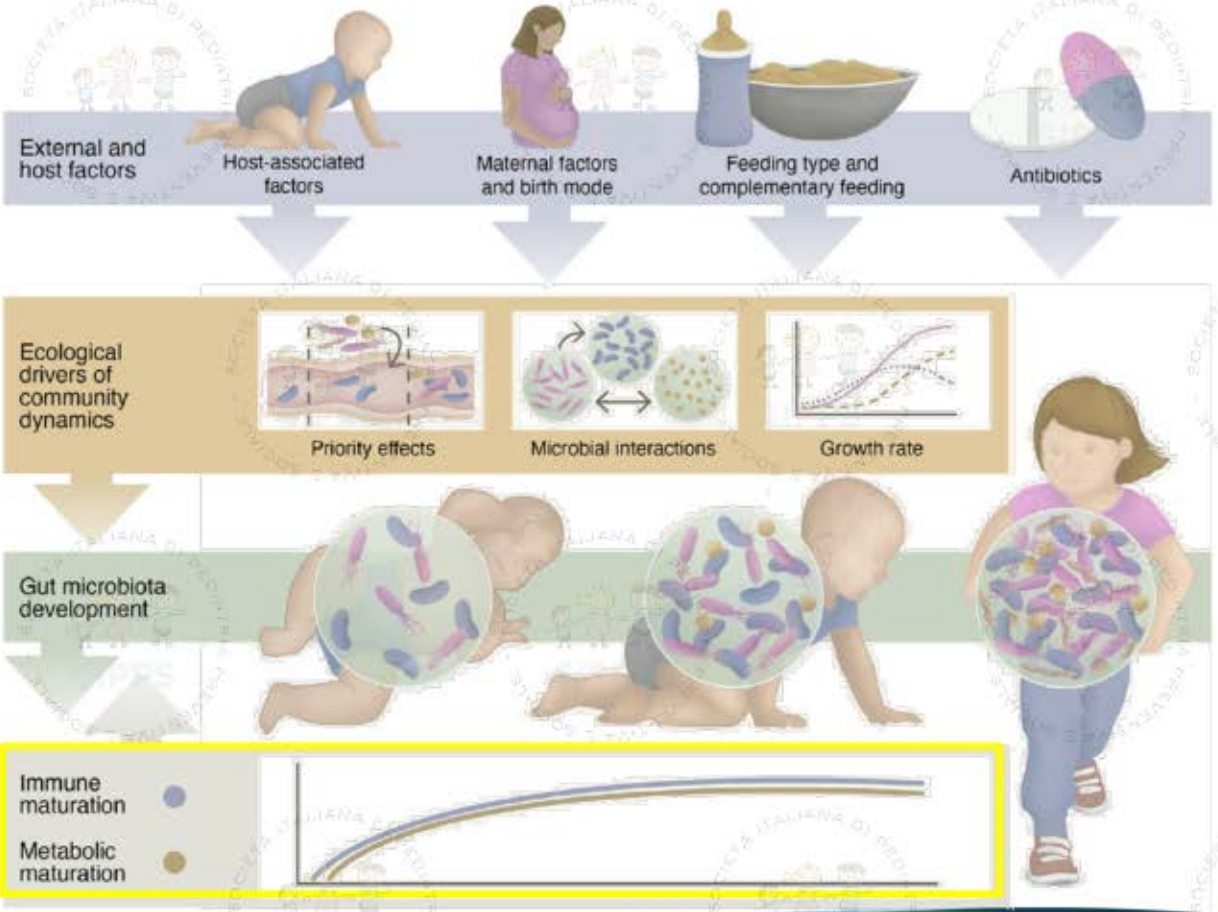
Tolerance

Metabolism

Digestion and absorption

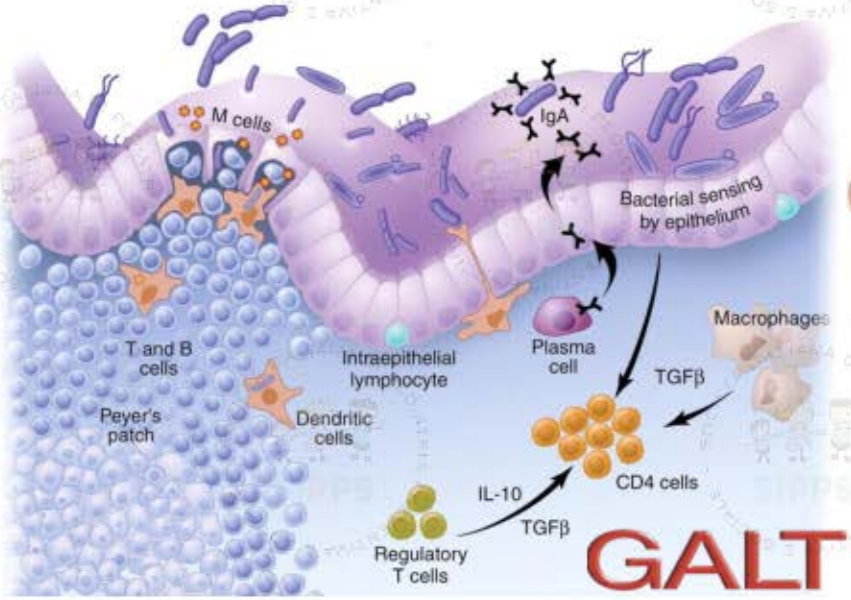
Gut - brain crosstalk

Satiety
Mood
Pain



C. Jian et al. / EBioMedicine (2021)

West CE, Jenmalm MC, Prescott SL. The gut microbiota and its role in the development of allergic disease: a wider perspective. Clin Exp Allergy 2014

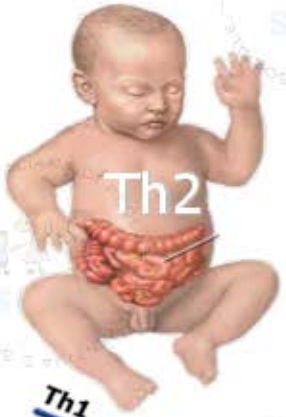


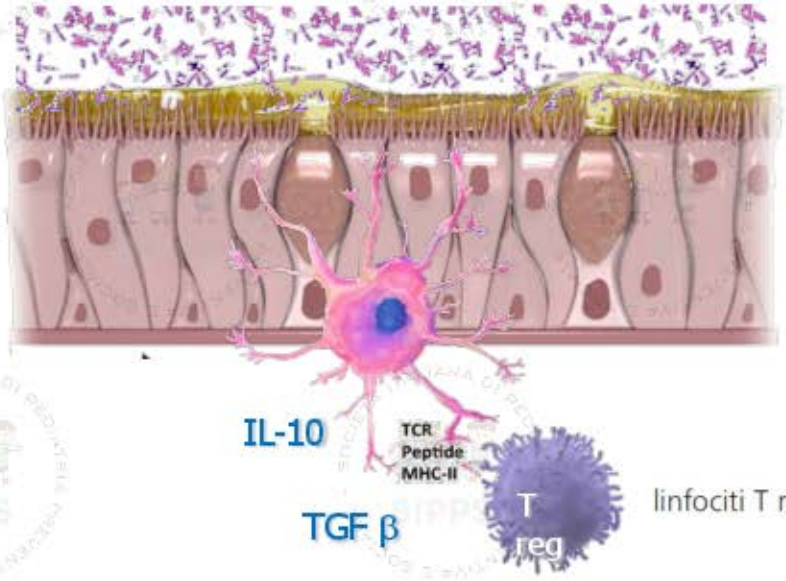
Gut-Associated Lymphoid Tissue

70%

della componente cellulare del sistema immunitario si trova nell'intestino

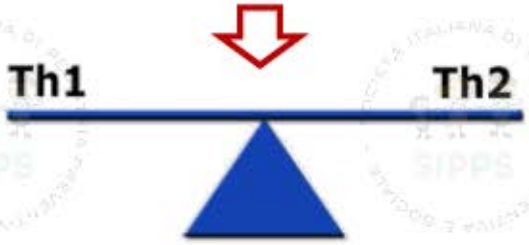
Il microbiota intestinale è un *organo batterico* **immuno-modulante**





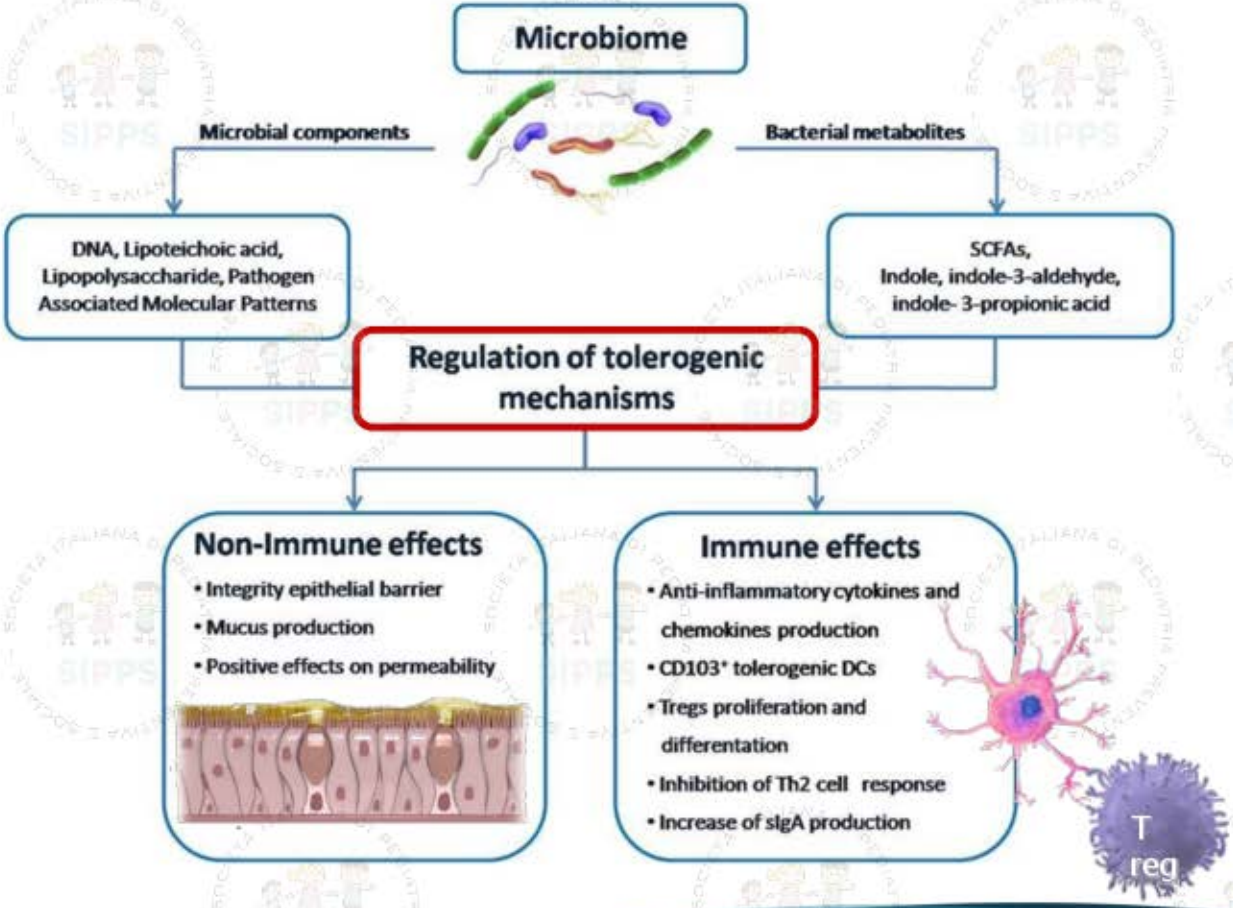
linfociti T regolatori (T_{reg})

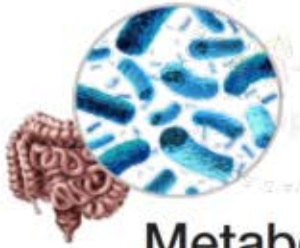
Malattie autoimmunitarie



Allergie

Il microbiota intestinale è un *organo batterico* con **funzione tollerogenica**


Microbiome
Microbial components
Bacterial metabolites
DNA, Lipoteichoic acid, Lipopolysaccharide, Pathogen Associated Molecular Patterns
SCFAs, Indole, indole-3-aldehyde, indole- 3-propionic acid
Regulation of tolerogenic mechanisms
Non-Immune effects
• Integrity epithelial barrier
• Mucus production
• Positive effects on permeability
Immune effects
• Anti-inflammatory cytokines and chemokines production
• CD103+ tolerogenic DCs
• Tregs proliferation and differentation
• Inhibition of Th2 cell response
• Increase of sIgA production
T reg



Metabolites

BSH: bile salt hydrolase

BSH-producing bacteria
(e.g. *Bifidobacterium* spp., *Bacteroides* spp.)

HMO-utilizing bacteria
(e.g. *Bifidobacterium* spp., *Bacteroides* spp.)

Gram-negative bacteria
(e.g. Proteobacteria, *Bacteroides* spp.)

Secondary bile acids

SCFAs

LPS

Satiety control

Lipid and glucose metabolism

Energy harvest and fat storage

Immune homeostasis and inflammation

Gut barrier function

C. Jian et al. / EBioMedicine 69 (2021)

L'organo fragile

Vito Leonardo Miniello

Sintesi InfoMedica

Journal of Probiotics & Health
ISSN: 2329-8901
Review Article

The Importance of Being Eubiotic 2017

Vito Leonardo Miniello[1], Lucia Diaferio[1], Carlotta Lassandro[2] and Elvira Verduci[2*]

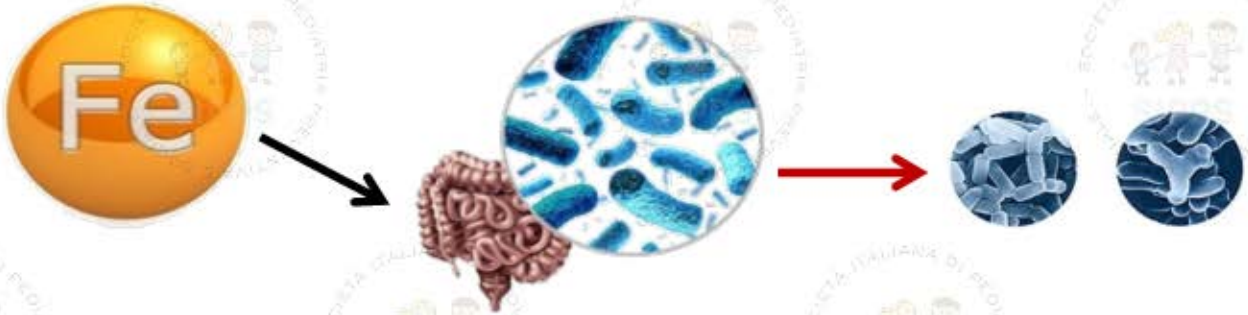
Modalità del **parto**

Modalità **allattamento**

Antibiotici Ferro PPI

Apgar score **LGA**

Miniello et al 2017



Complementary Feeding and Iron Status: *"The Unbearable Lightness of Being"* Infants

Vito Leonardo Miniello [1,*], Maria Carmen Verga [2], Andrea Miniello [3], Cristina Di Mauro [4], Lucia Diaferio [5] and Ruggiero Francavilla [6]

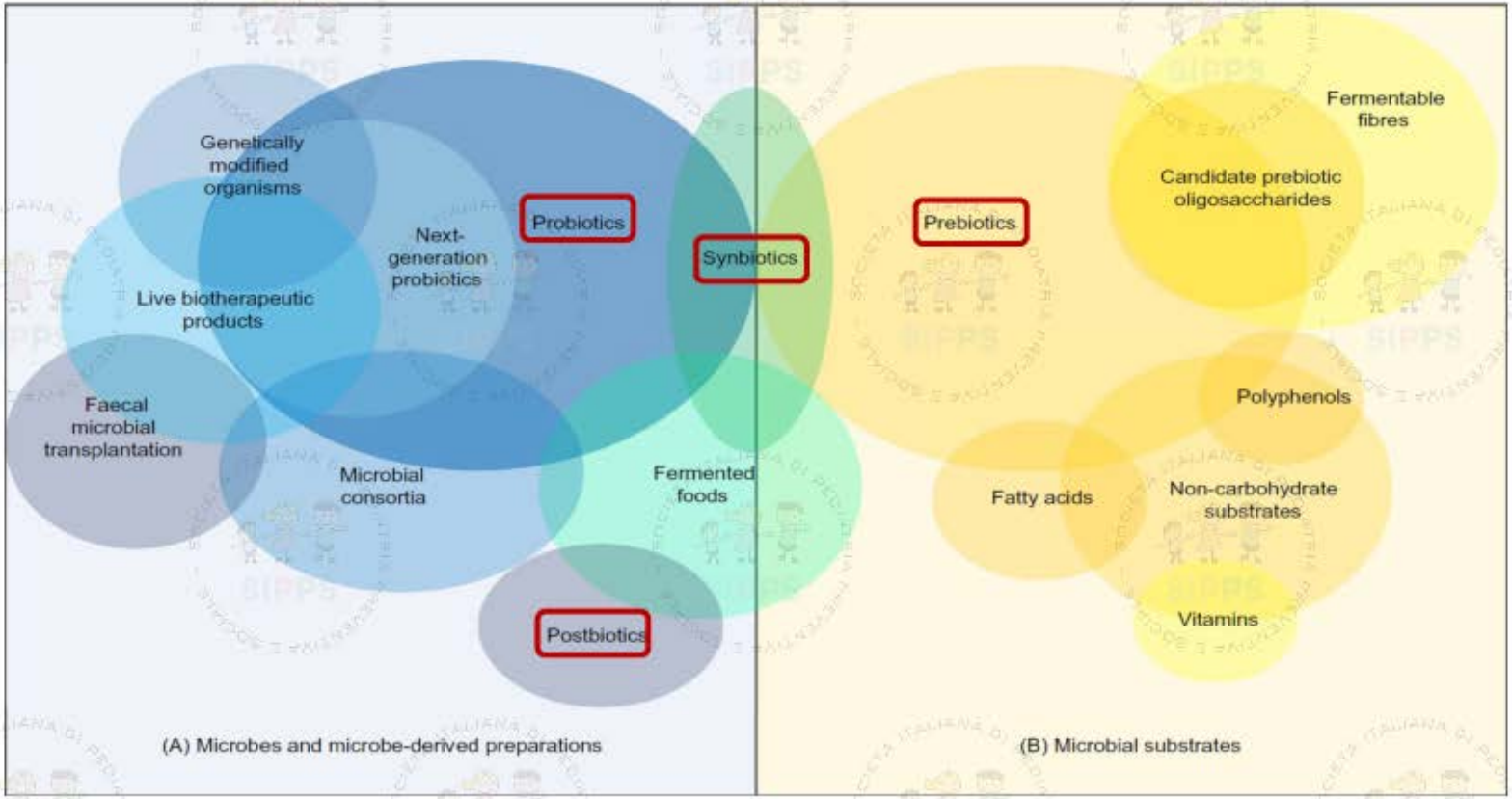
Nutrients **2021**


BIOMODULATORI
DEL MICROBIOTA
INTESTINALE:
tra realtà e futuro
Vito Leonardo Miniello
EDITEAM

Biomodulatori del microbiota intestinale

PROBIOTICI	Microrganismi vivi che, assunti in quantità adeguata, conferiscono all'organismo ospite effetti benefici sulla salute
PREBIOTICI	Substrati selettivamente utilizzati dai microrganismi indigeni in grado di indurre effetti benefici sulla salute
SIMBIOTICI	Associazione di prebiotici e probiotici
POSTBIOTICI	Prodotti batterici o derivati metabolici di microrganismi probiotici con attività biologica per l'ospite

Shaping the Future of Probiotics and Prebiotics



M. Cunningham Trends in Microbiology, August 2021

Shaping the Future of Probiotics and Prebiotics

Trends in Microbiology

FDA
The Food and Drug Administration

efsa
European Food Safety Authority

Generally recognised as safe (GRAS): a notification to the FDA stating that a substance is generally recognised, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.

Qualified presumption of safety (QPS): a status granted to genera, species, or subspecies of microorganisms by the EFSA after an application is received and an assessment of available evidence on characterisation, safety, and intended use is conducted.

M. Cunningham Trends in Microbiology, August 2021

novel regulatory frameworks are emerging

FDA
The Food and Drug Administration

edqm
European Directorate for the Quality of Medicines & HealthCare

Live biotherapeutic products:
biological products that contains live organisms and are applicable to the prevention, treatment, or cure of a disease.

European Pharmacopoeia Commission (2019) 3053E General monograph on live biotherapeutic products. *Eur. Pharmacopoeia*

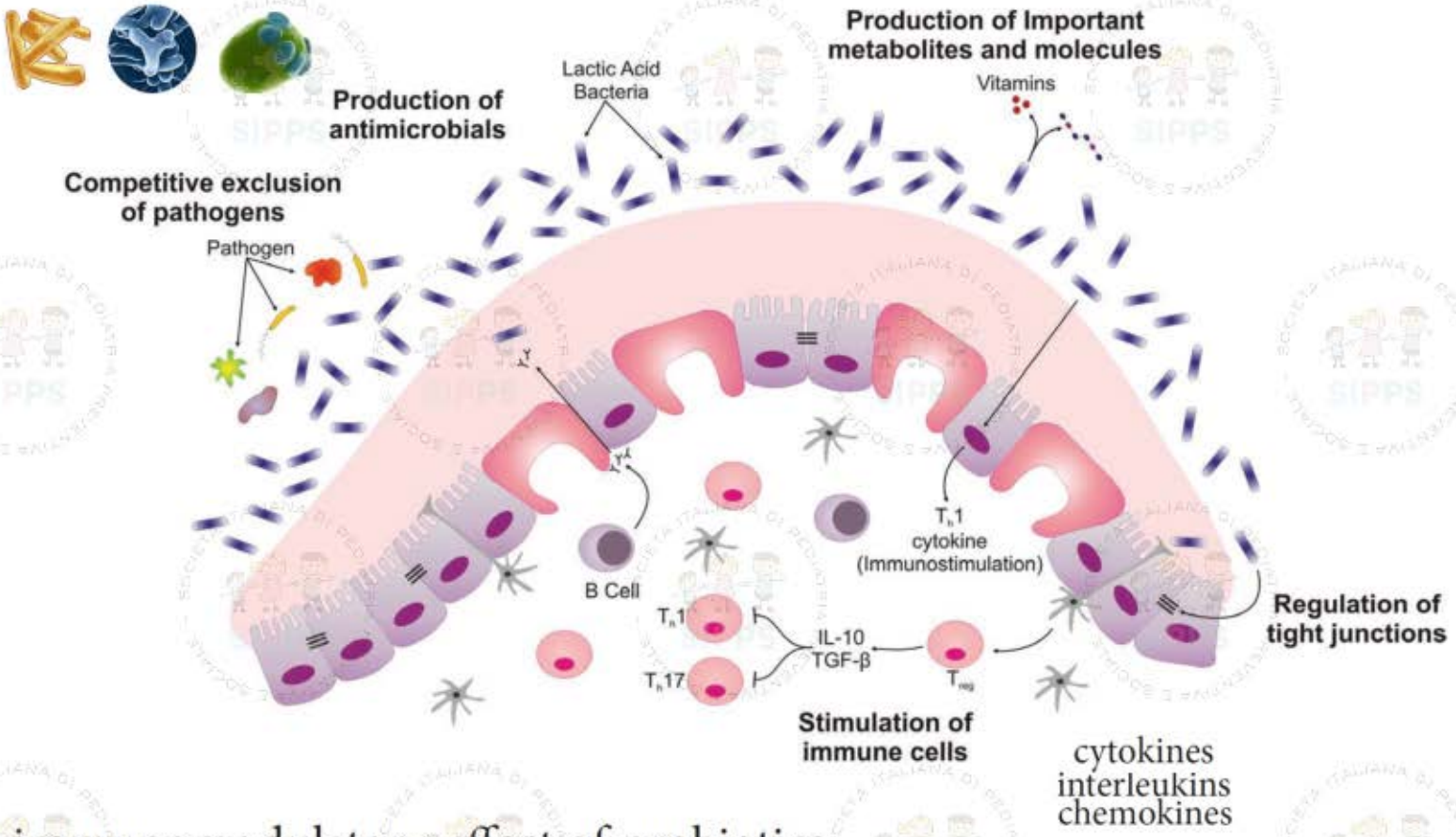
M. Cunningham Trends in Microbiology, August 2021

Probiotics for human use

Nutrition Bulletin 2018

M. E. Sanders*, D. Merenstein†, C. A. Merrifield‡ and R. Hutkins§

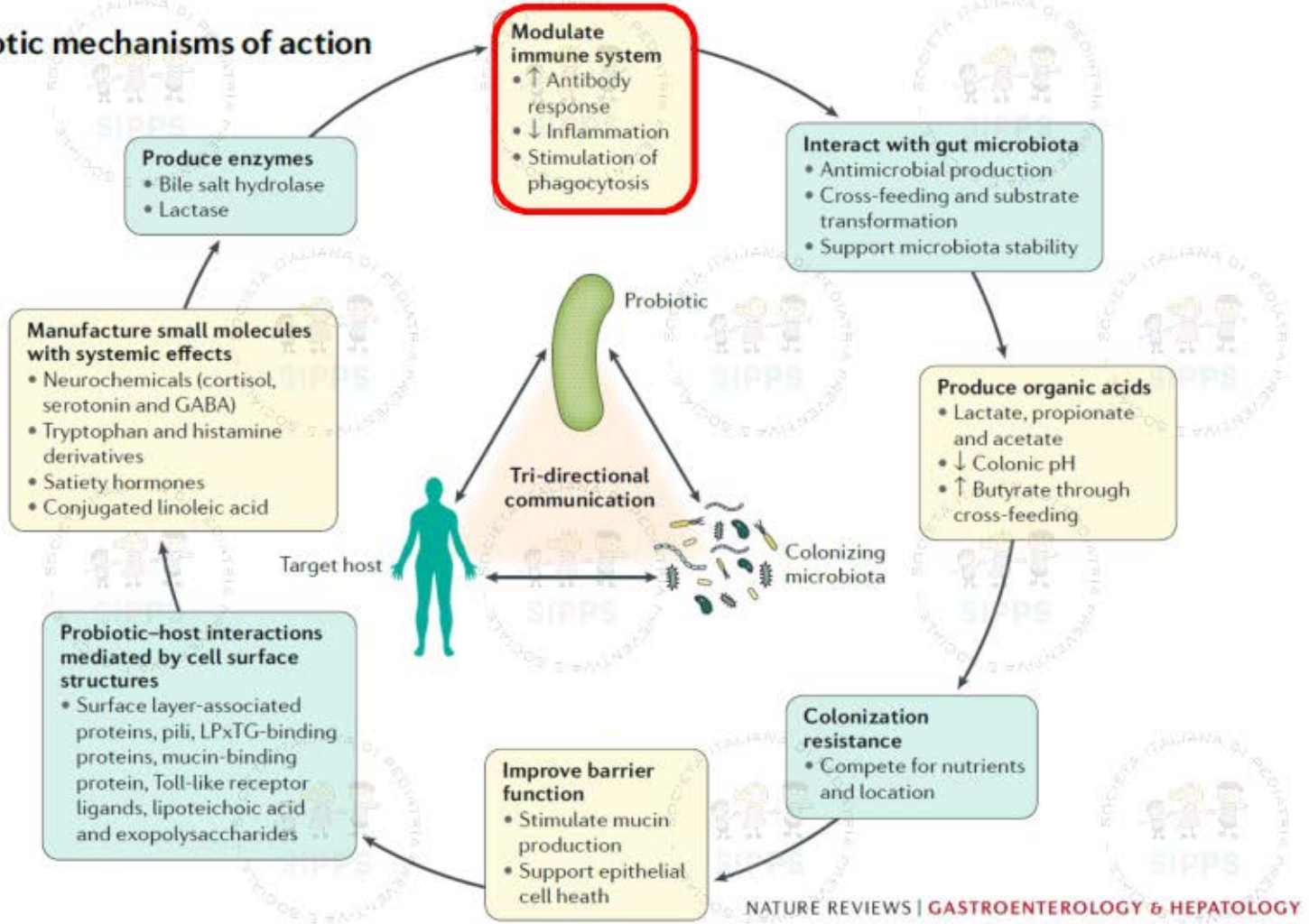
'Probiotics' comprise many different types of microbes. It is important, therefore, to remember that they are described by their genus, species and strain designations. Using the example of one well-studied probiotic, *Lactobacillus rhamnosus* GG – *Lactobacillus* is the genus, *rhamnosus* is the species and GG is the strain designation. All three components are necessary to identify a probiotic.



immunomodulatory effect of probiotics

Ghosh Frontiers in Microbiology *2019*

Probiotic mechanisms of action



NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

Sanders 2019

Rare
Strain-specific effects

- Neurological effects
- Immunological effects
- Endocrinological effects
- Production of specific bioactives

Frequent
Species-level effects

- Vitamin synthesis
- Direct antagonism
- Gut barrier reinforcement
- Bile salt metabolism
- Enzymatic activity
- Neutralization of carcinogens

Widespread
Among studied probiotics

- Colonization resistance
- Acid and SCFA production
- Regulation of intestinal transit
- Normalization of perturbed microbiota
- Increased turnover of enterocytes
- Competitive exclusion of pathogens

Rare
Strain-specific effects

- Neurological effects
- Immunological effects
- Endocrinological effects
- Production of specific bioactives

D. Haller, C. Bode, W. P. Hammes, A. M. A. Pfeifer, E. J. Schiffrin, and S. Blum, "Non-pathogenic bacteria elicit a differential cytokine response by intestinal epithelial cell/leucocyte co-cultures," *Gut*, vol. 47, no. 1, pp. 79–87, 2000.

In an *in vitro* study with Caco-2 cells , proinflammatory cytokines (IL-1β, IL-8, and TNF-α) were induced by *Lactobacillus sakei*, whereas *Lactobacillus johnsonii* influenced the production of TGF-β (anti-inflammatory).

Probiotics in Autoimmune and Inflammatory Disorders

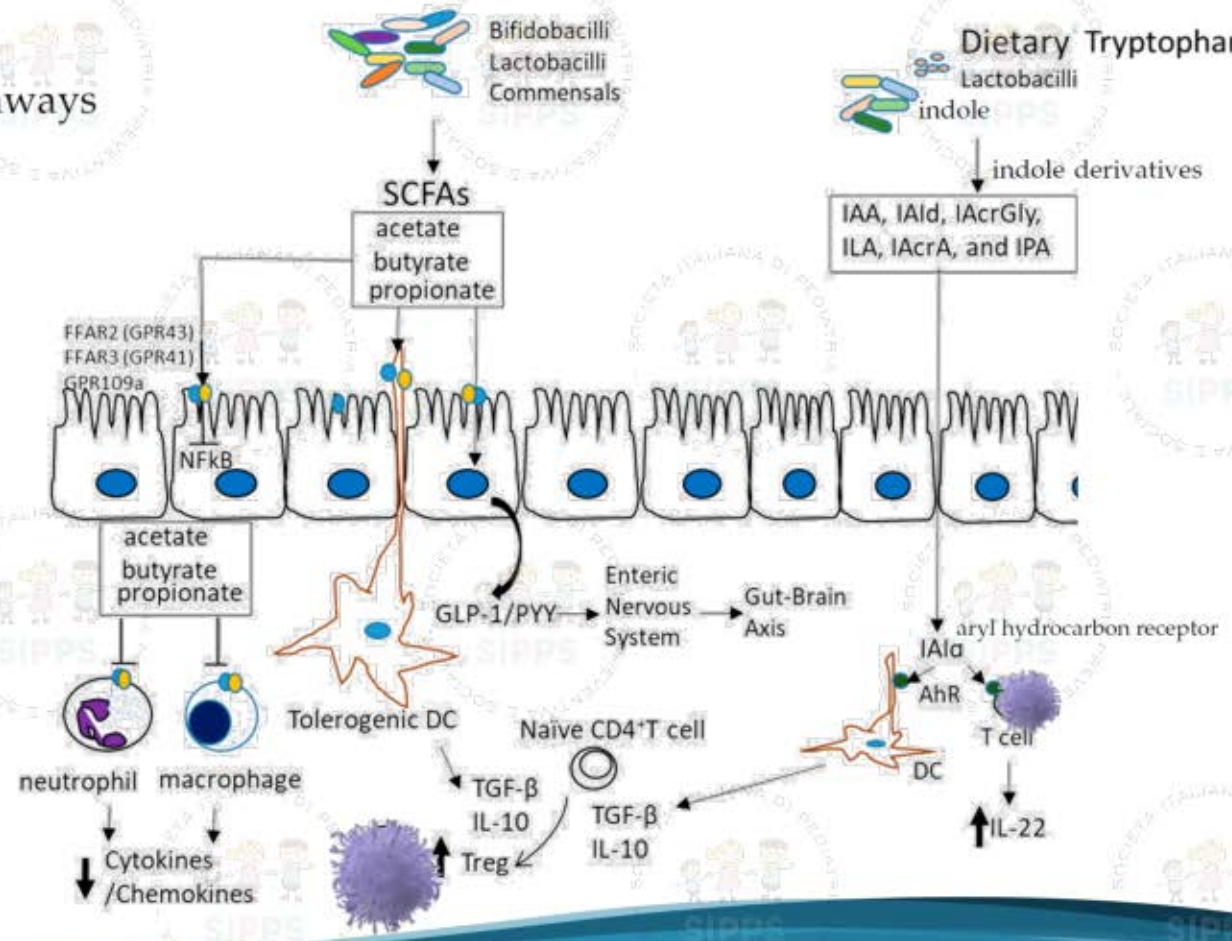
Critical metabolites produced by probiotics which have anti-inflammatory functions.

4

metabolic pathways

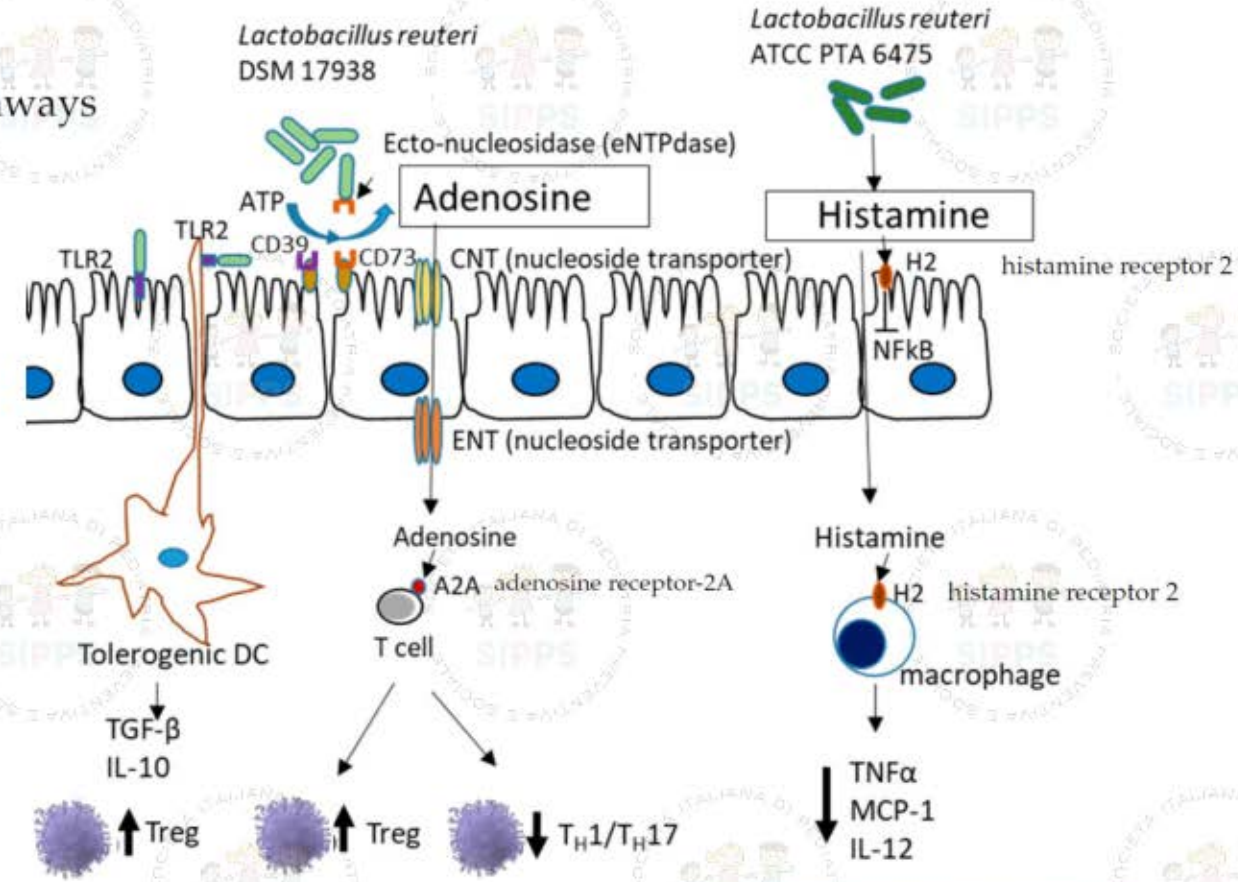
Yuying.Liu *Nutrients* 2018

4 metabolic pathways



Yuying.Liu *Nutrients* 2018

4 metabolic pathways



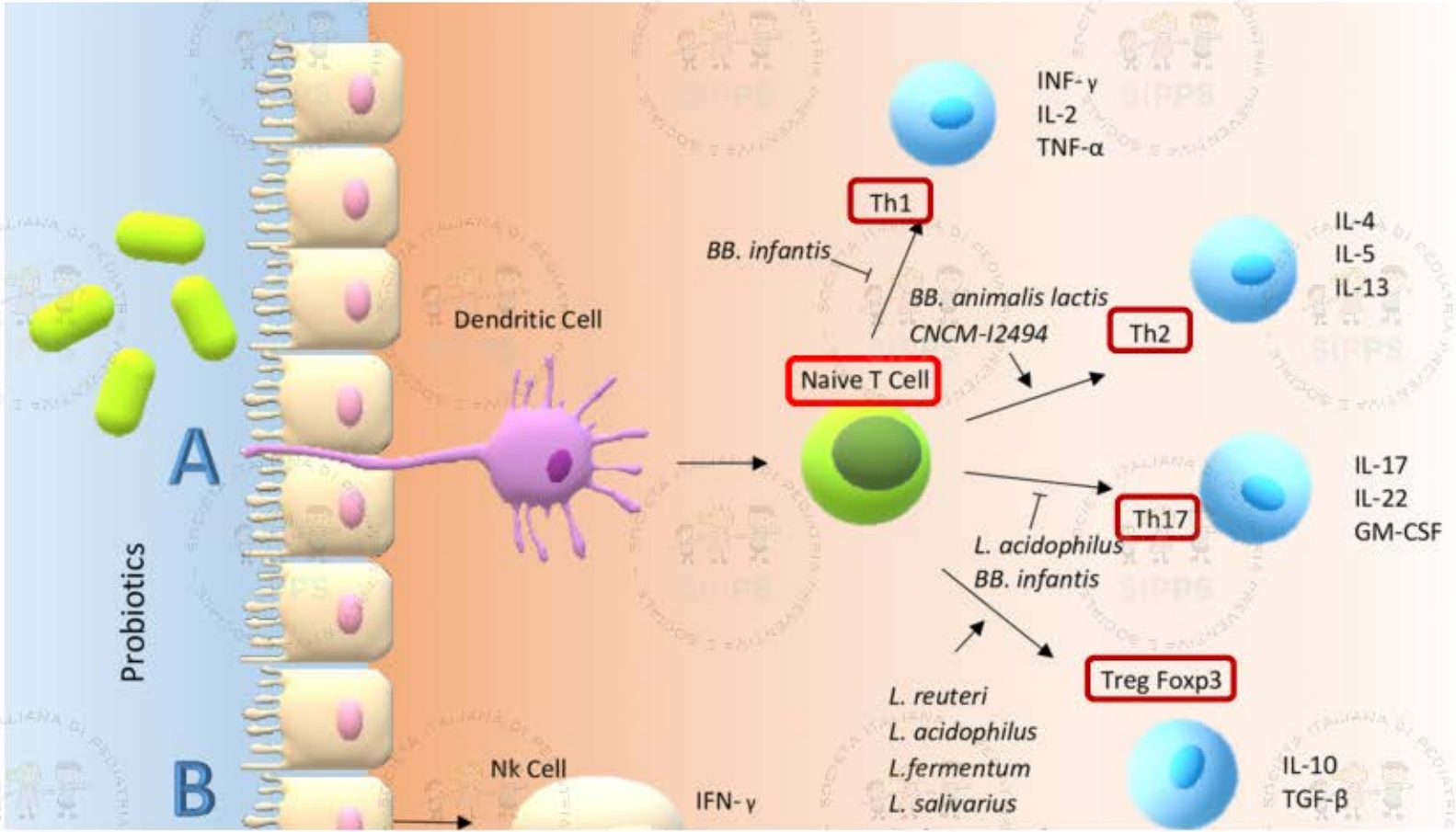
Yuying.Liu *Nutrients* **2018**


TIME
BUSH'S MILITARY RECORDS IS DISNEY MOUSETRAPPED?
THE SECRET KILLER
The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases
What you can do to fight it

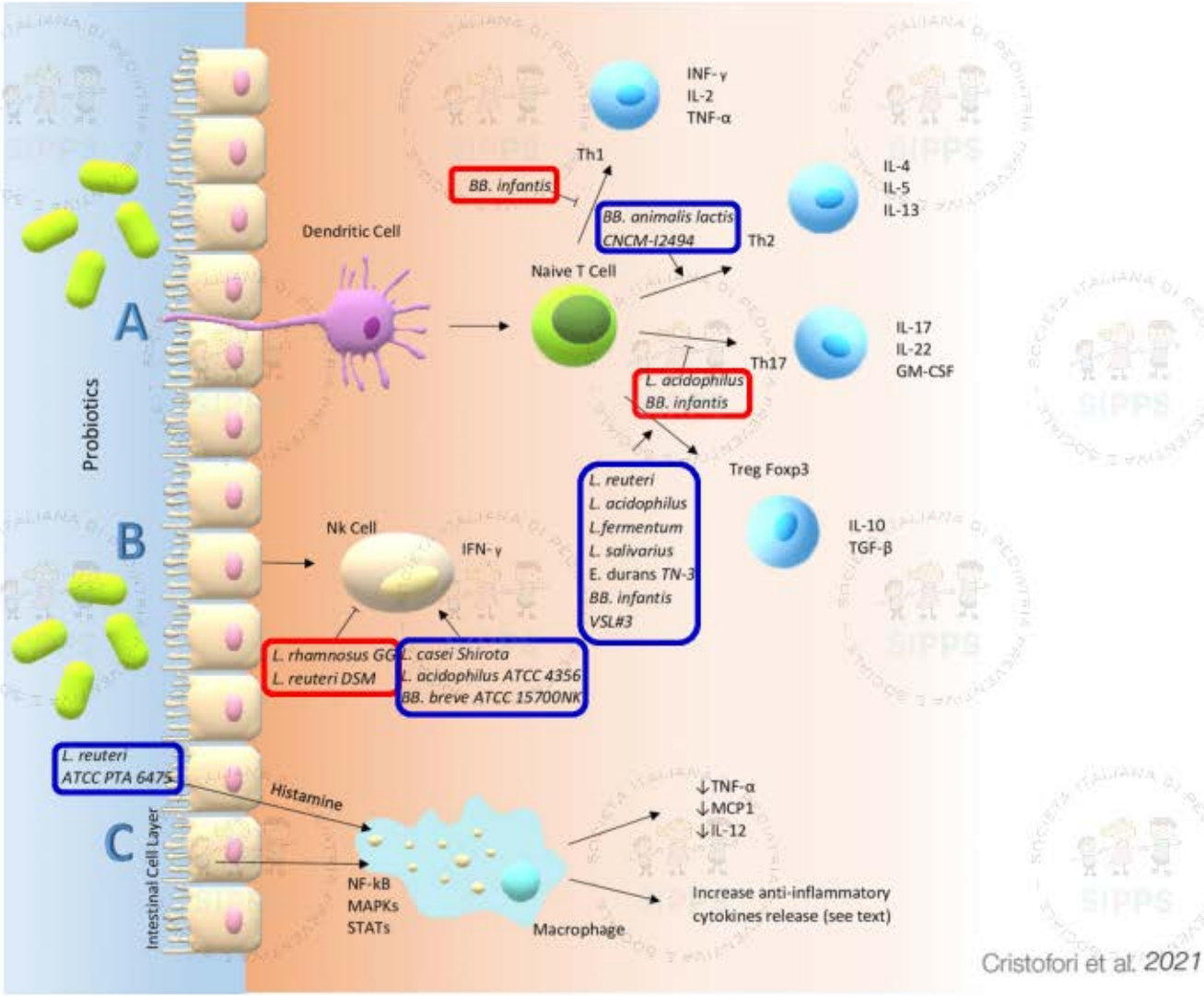
Anti-Inflammatory and Immunomodulatory Effects of Probiotics in Gut Inflammation: A Door to the Body

frontiers in Immunology 2021

*Fernanda Cristofori[1], Vanessa Nadia Dargenio[1], Costantino Dargenio[1], Vito Leonardo Miniello[1], Michele Barone[2] and Ruggiero Francavilla[1]**



Cristofori et al. *2021*



Cristofori et al. *2021*

Probiotics in Preventing Acute Upper Respiratory Tract Infections

Cochrane Library

13 RCTs 3,720 participants in RCTs

Probiotics were found to be more effective than placebo—reducing the number of participants who experienced episodes of acute URTI by about 47% and the duration of an episode by about 1.89 days.

Probiotics are likely more effective than placebo in reducing the number of episodes of acute URTI, the average duration of these episodes, antibiotic use, and URTI-related school absences.

However, the quality of the evidence was low or very low.

Hao Q et al. 2016

Prevention of recurrent respiratory infections

Chiappini *et al. Italian Journal of Pediatrics* 2021

Inter-society Consensus

Elena Chiappini[1*], Francesca Santamaria[2], Gian Luigi Marseglia[3], Paola Marchisio[4], Luisa Galli[1], Renato Cutrera[5], Maurizio de Martino[1], Sara Antonini[1], Paolo Becherucci[6], Paolo Biasci[7], Barbara Bortone[1], Sergio Bottero[8], Valeria Caldarelli[9], Fabio Cardinale[10], Guido Castelli Gattinara[11], Martina Ciarcià[1], Daniele Ciofi[1], Sofia D'Elios[12], Giuseppe Di Mauro[13], Mattia Doria[14], Luciana Indinnimeo[15], Andrea Lo Vecchio[2], Francesco Macrì[16], Roberto Mattina[17], Vito Leonardo Miniello[18], Michele Miraglia del Giudice[19], Guido Morbin[20], Marco Antonio Motisi[1], Andrea Novelli[1], Anna Teresa Palamara[21], Maria Laura Panatta[22], Angela Pasinato[23], Diego Peroni[12], Katia Perruccio[24], Giorgio Piacentini[25], Massimo Pifferi[26], Lorenzo Pignataro[4], Emanuela Sitzia[22], Chiara Tersigni[1], Sara Torretta[4], Irene Trambusti[12], Giulia Trippella[1], Diletta Valentini[27], Sandro Valentini[28], Attilio Varricchio[29], Maria Carmen Verga[30], Claudio Vicini[31], Marco Zecca[32] and Alberto Villani[27]

Prevention of recurrent respiratory infections

Inter-society Consensus

Società Scientifiche, Federazioni ed Associazioni rappresentate:

Società Italiana di Pediatria (SIP)

Federazione Italiana Medici Pediatri (FIMP)

Società Italiana di Malattie Respiratorie Infantili (SIMRI)

Società di Malattie Infettive Pediatriche (SITIP)

Società Italiana di Pediatria Preventiva e Sociale (SIPPS)

Società Italiana di Allergologia e Immunologia Pediatria (SIAIP)

Società Italiana di Otorinolaringoiatria Pediatrica (SIOP)

Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP)

Società Italiana delle Cure Primarie Pediatriche (SICuPP)

Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-facciale (SIO e ChCF)

Società Italiana di Microbiologia (SIM)

Società Italiana di Chemioterapia (SIC)

Società Italiana di Pediatria Infermieristica (SIPINF)

Prevention of recurrent respiratory infections

Probiotics, Prebiotics, Symbiotics, Postbiotics

In the absence of proof of efficacy, the use of oral probiotic formulations should not be recommended for the prevention of RRIs (**weak negative recommendation**).

Given the scarcity of supporting evidence, the use of nasal spray formulations containing *Streptococcus salivarius* 24SMB should not be recommended for the prevention of RRIs (**weak negative recommendation**).

In the absence of proof of efficacy and safety, the use of prebiotics and symbiotics should not be recommended for the prevention of RRIs (**weak negative recommendation**).

In the absence of proof of efficacy and safety, the use of postbiotics should not be recommended for the prevention of RRIs (**weak negative recommendation**).

Chiappini *et al. Italian Journal of Pediatrics* 2021

in infancy

atopic dermatitis

food allergy

in childhood

allergic asthma

allergic rhinitis

atopic march

skin barrier damage: TSLP, IL-33,IL-25 ↑ filaggrin ↓

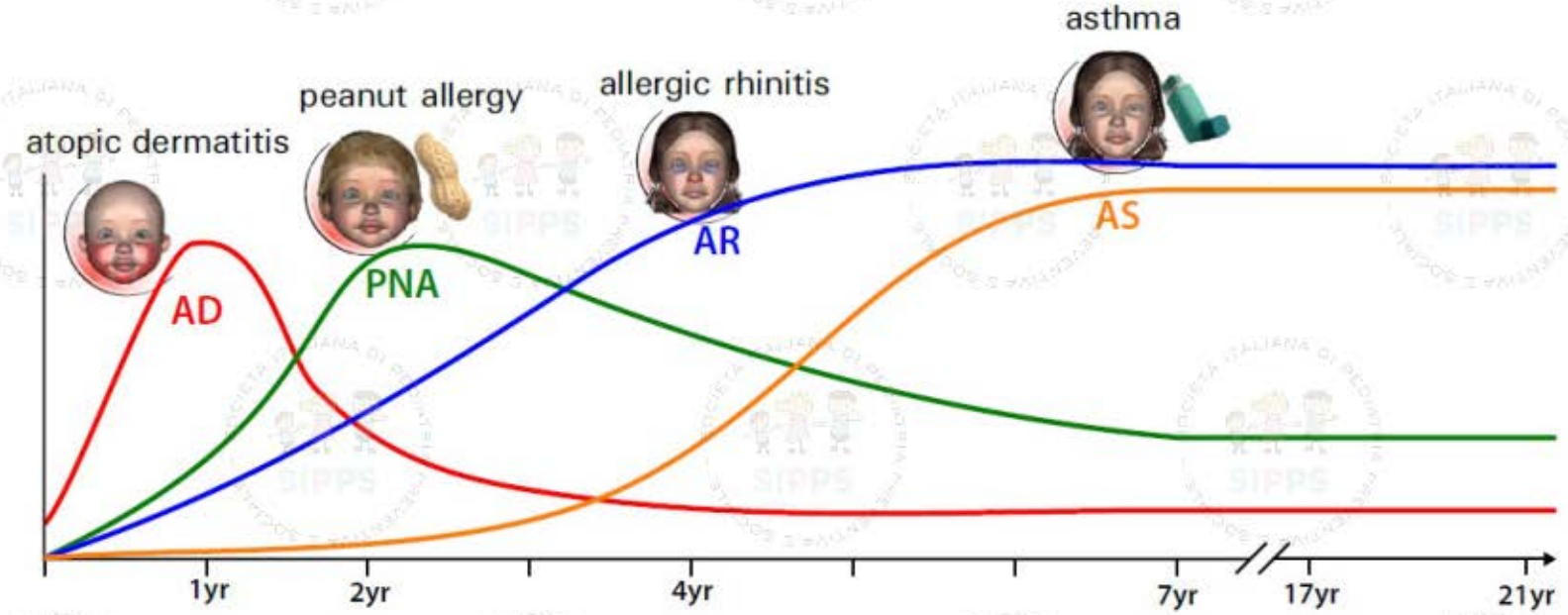
microbiome alteration

interference of predicted genes

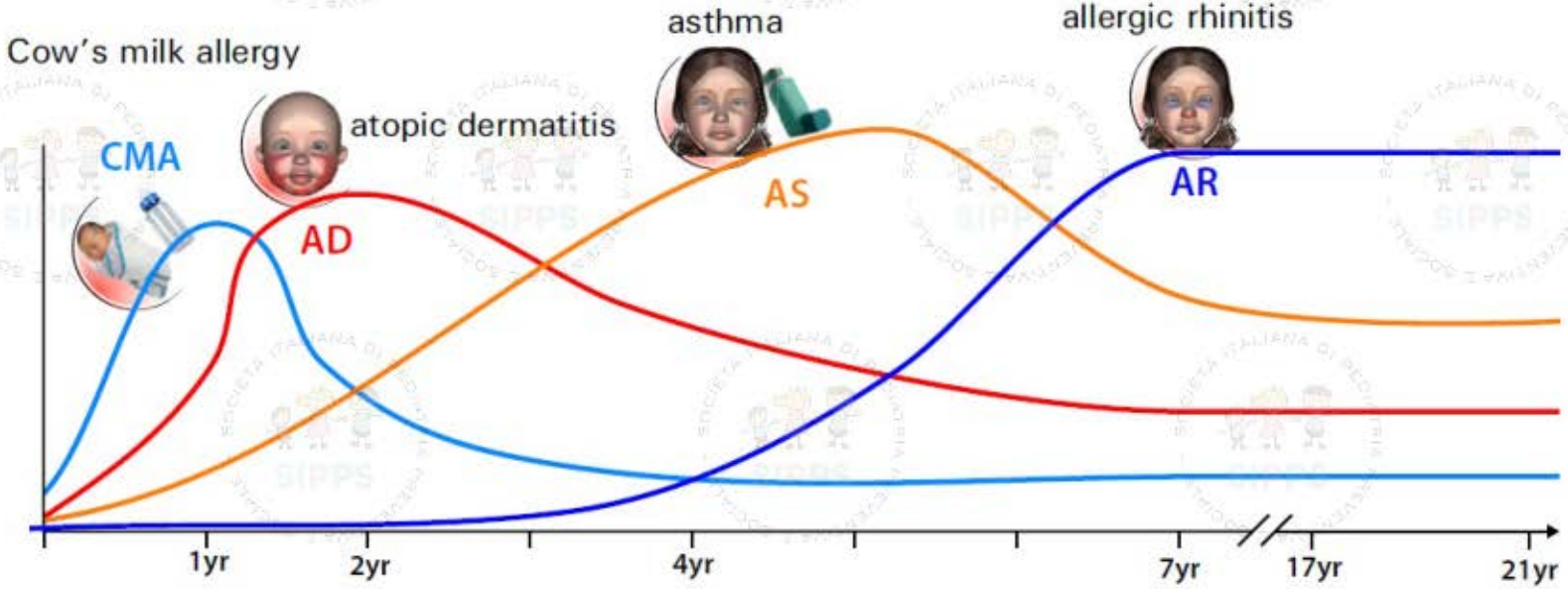
"social" dysfunction of cells and molecules

epigenetic factors

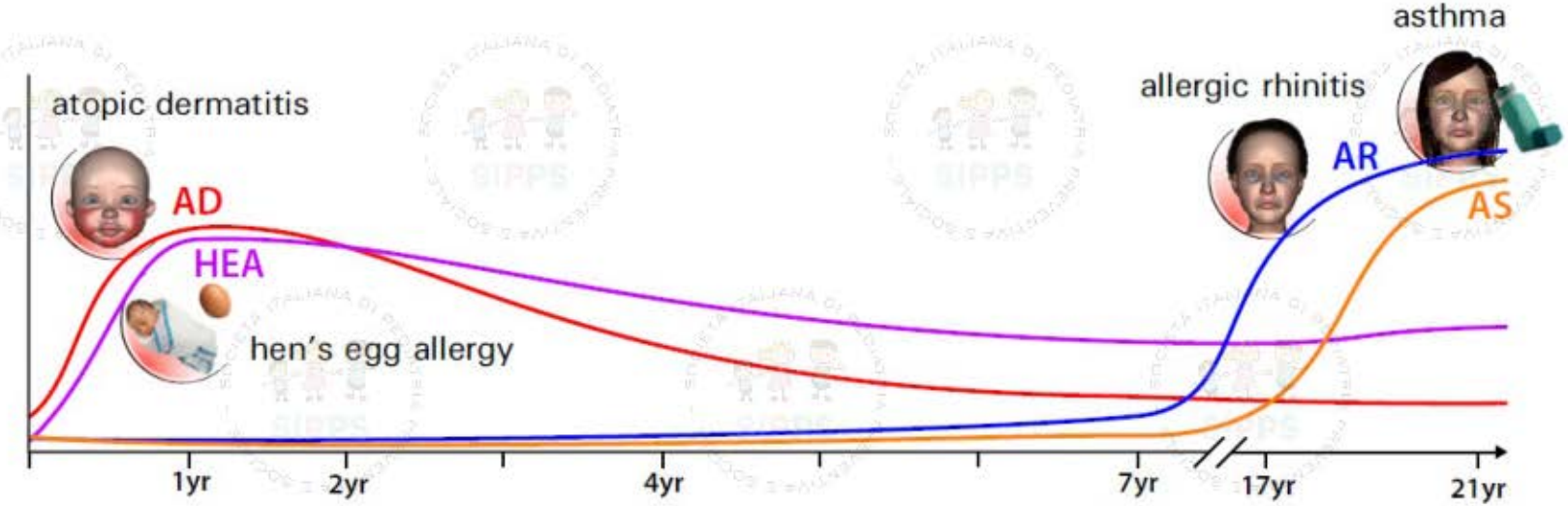
Yang et al Frontiers in Immunology 2020



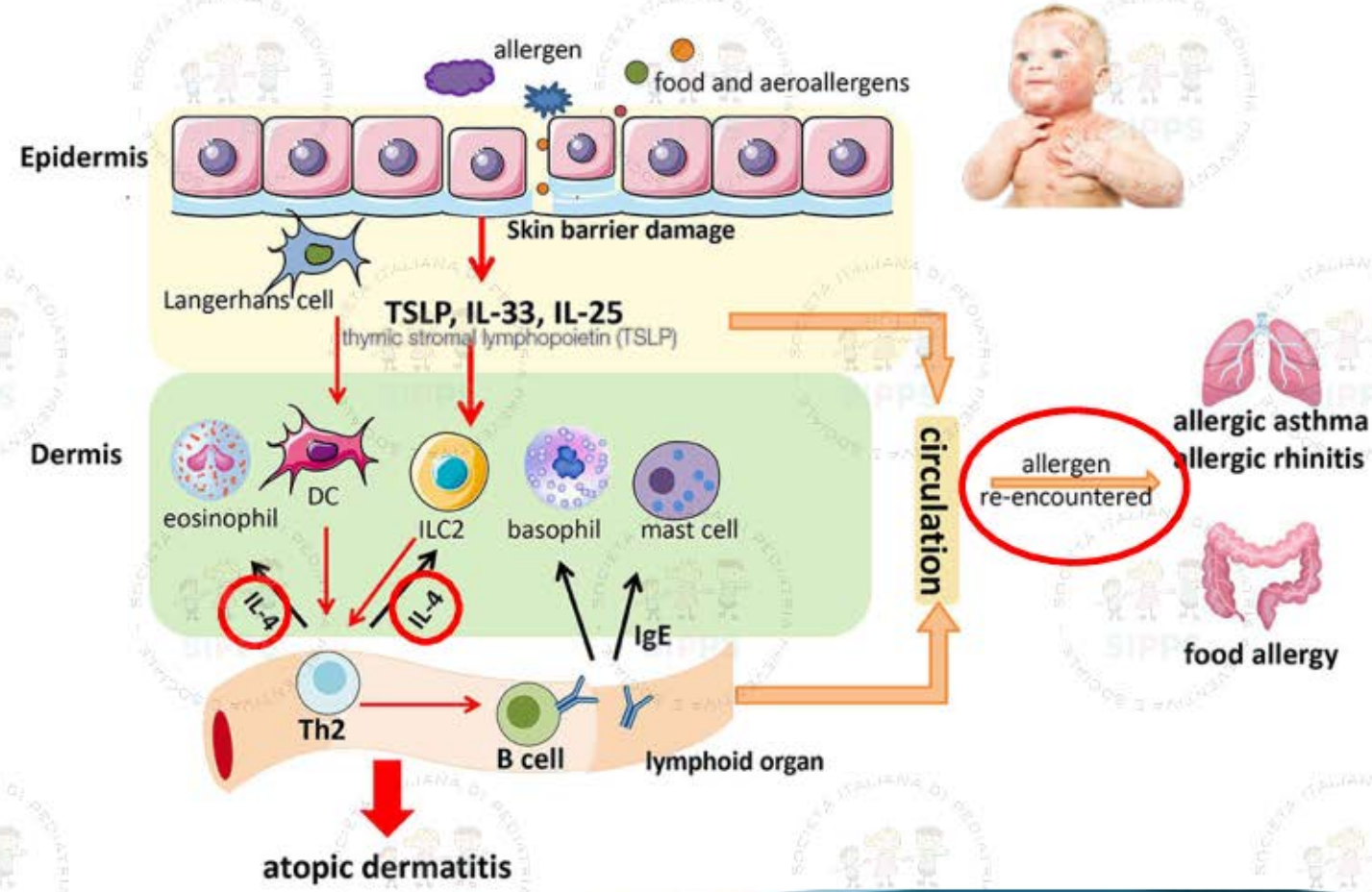
BAWANY ET AL J ALLERGY CLIN IMMUNOL PRACT 2020



BAWANY ET AL J ALLERGY CLIN IMMUNOL PRACT 2020



BAWANY ET AL J ALLERGY CLIN IMMUNOL PRACT 2020



Yang et al Frontiers in Immunology 2020

microbiota


Skin
Large intestine
Oral cavity
Lung and respiratory tract
Stomach and distal esophagus
Vagina

Lactobacillus reuteri Modulates Cytokines Production in Exhaled Breath Condensate of Children With Atopic Dermatitis

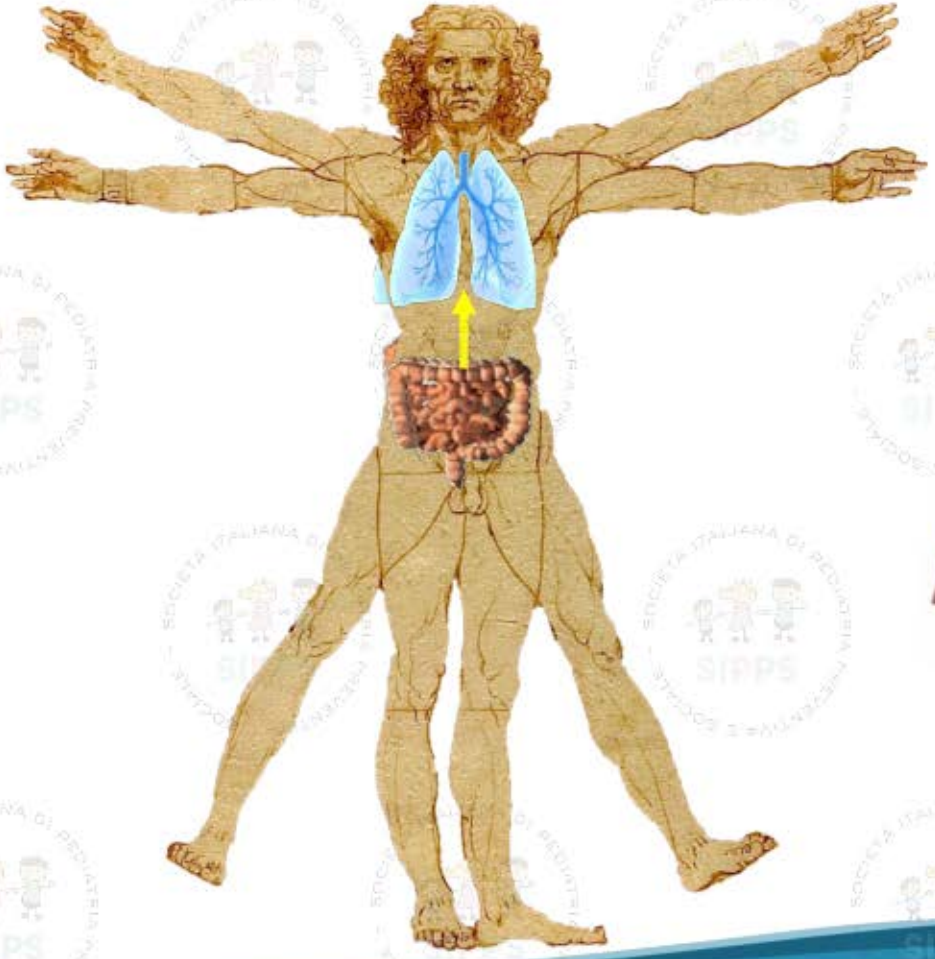
Vito Leonardo Miniello, Luigia Brunetti, Riccardina Tesse, Miria Natile, Lucio Armenio, and Ruggiero Francavilla

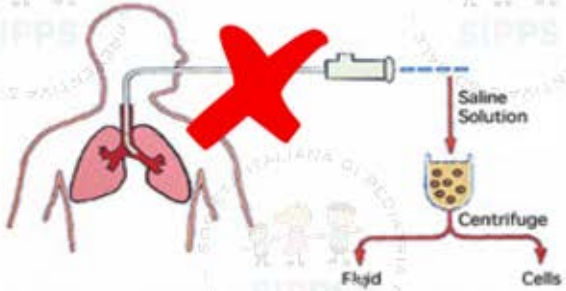
JPGN 2010

Dermatite ATOPICA
Eczema NON atopico

SCORAD

IFN-γ IL-4
(nell'esalato condensato)




Saline
Solution
Centrifuge
Fluid
Cells

Lactobacillus reuteri ATCC 55730

Patients with AD receiving *Lactobacillus reuteri*	Patients with AD receiving placebo

Patients with nonatopic eczema receiving *Lactobacillus reuteri*	Patients with nonatopic eczema receiving placebo

Miniello et al

SCORAD Calculator - SCORing Atopic Dermatitis

	Patients with AD receiving *Lactobacillus reuteri*	Patients with AD receiving placebo	Patients with nonatopic eczema receiving *Lactobacillus reuteri*	Patients with nonatopic eczema receiving placebo
SCORAD index at inclusion (range)	27 (21–44)	31 (23–50)	35 (23–47)	33 (27–50)
SCORAD index after intervention (range)	25 (21–42)	27 (22–47)	31 (21–43)	34 (25–49)

After 8 weeks of treatment, no significant changes in the Severity Scoring Index Atopic Dermatitis Index mean values were observed in patients who received the probiotic supplementation compared with children who received placebo

We measured the concentration of interferon-γ and interleukin-4 in the exhaled breath condensate of children with atopic and nonallergic dermatitis receiving a probiotic supplementation (*Lactobacillus reuteri* ATCC 55730) or placebo for 8 weeks.

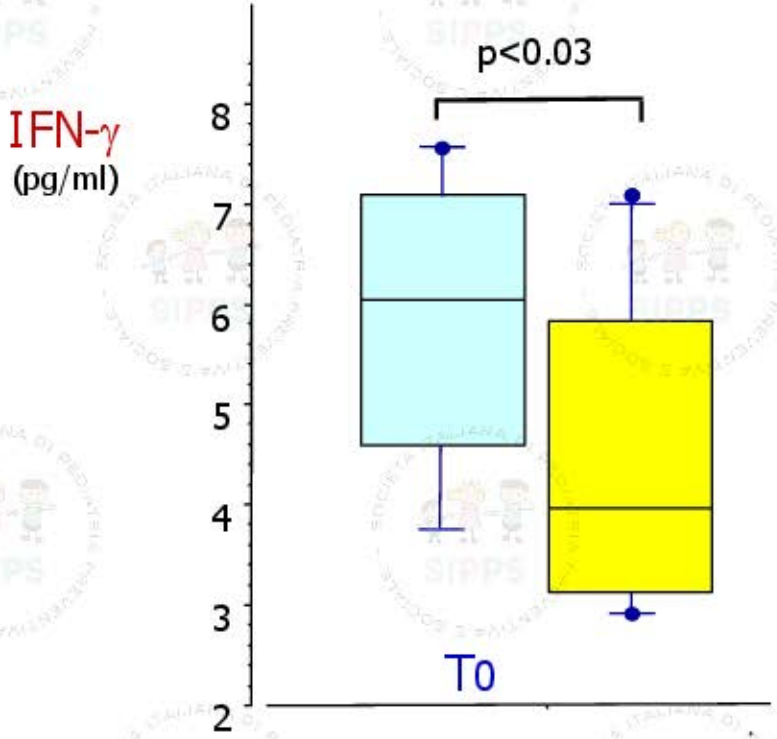
Miniello et al

INF-γ
IL-2
TNF-α

IL-4
IL-5
IL-13

IL-17
IL-22
GM-CSF

IFN-γ nell'esalato condensato



NON atopici

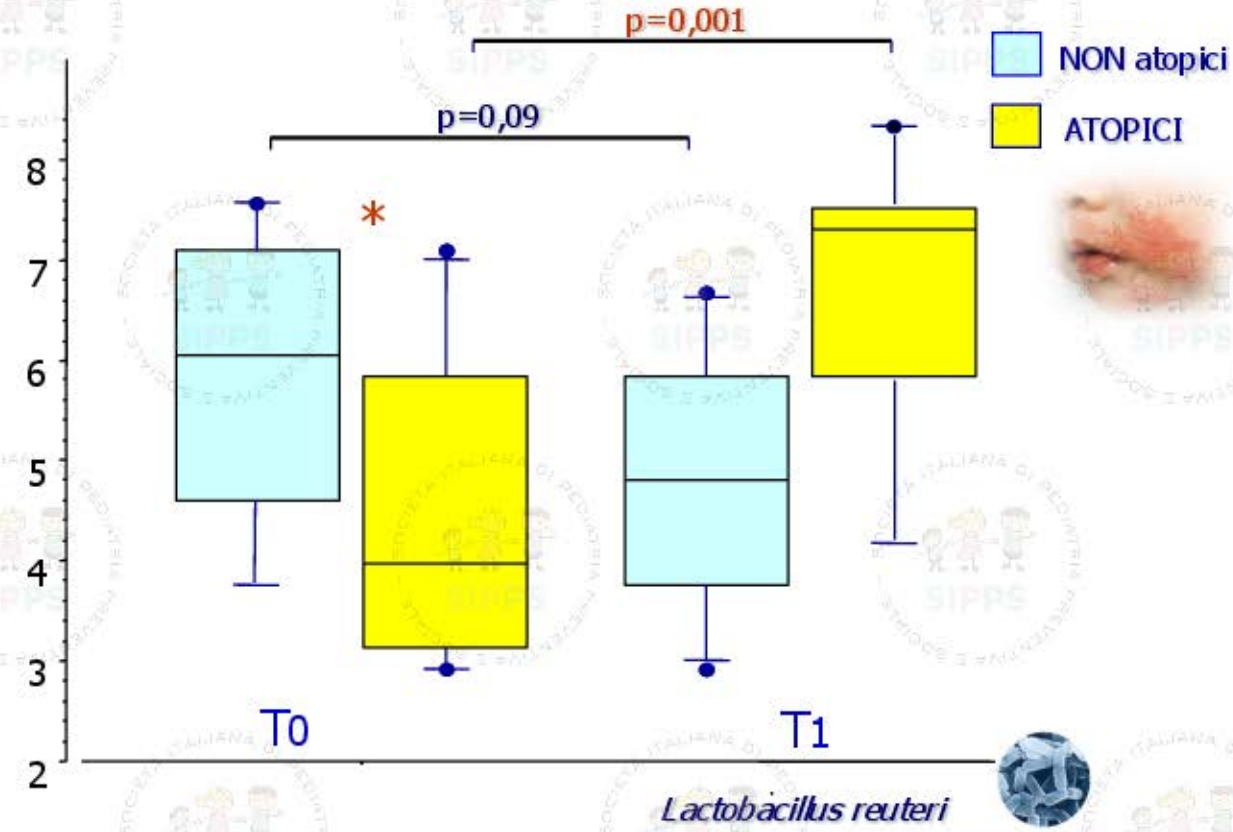
ATOPICI

Miniello et al

IFN-γ nell'esalato condensato

IFN-γ
(pg/ml)

* p<0.03

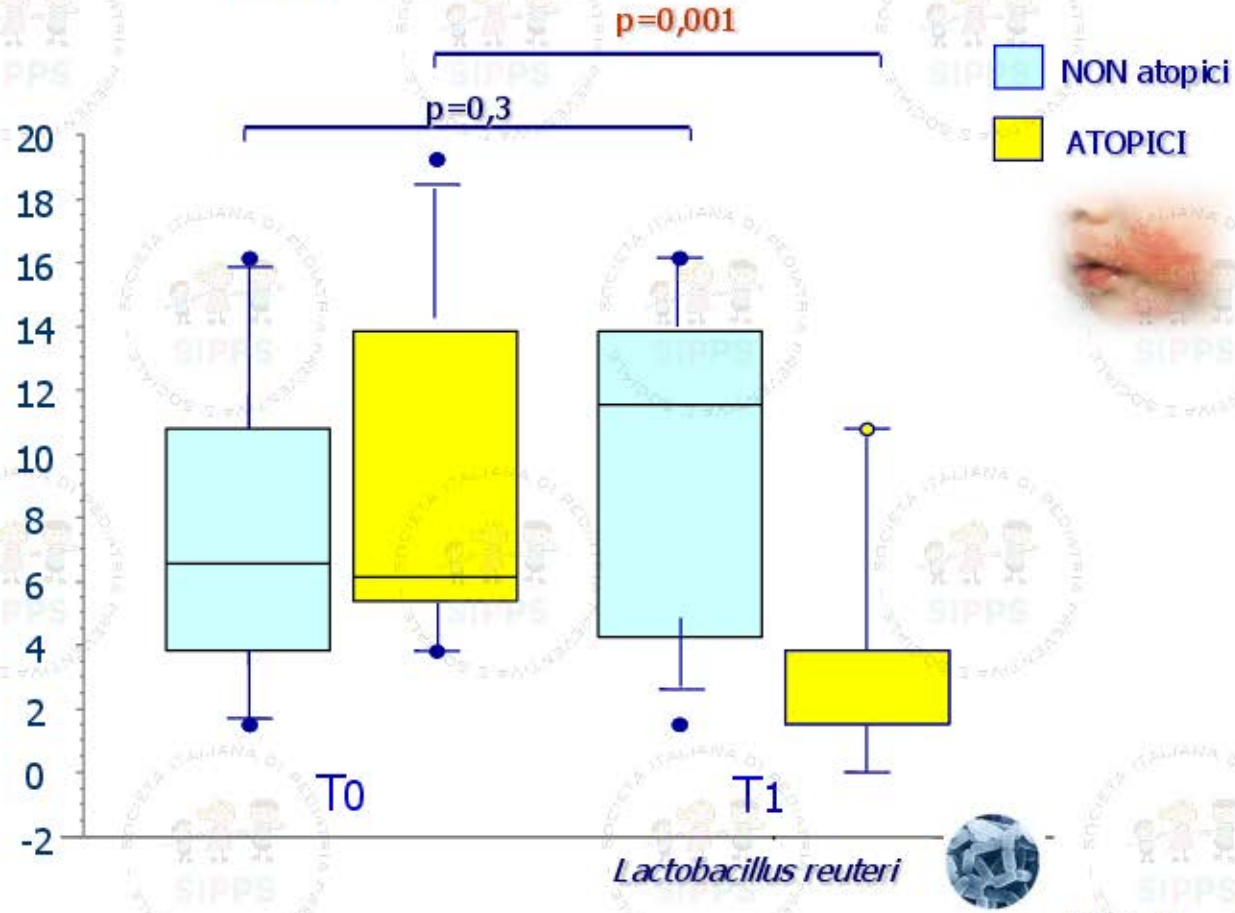


Lactobacillus reuteri

Miniello et al

IL-4 nell'esalato condensato

IL-4
(pg/ml)



Miniello et al

The Role of Probiotics in the Prevention and Treatment of Atopic Dermatitis in Children: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

Probiotics in Atopic Dermatitis in Children

Our updated meta-analysis demonstrates that intervention with probiotics potentially lowers the incidence of AD and relieve AD symptoms in children, particularly in infants and children aged ≥ 1 year. Interventions using mixed-strain probiotics tended to show better preventive and curative effects.

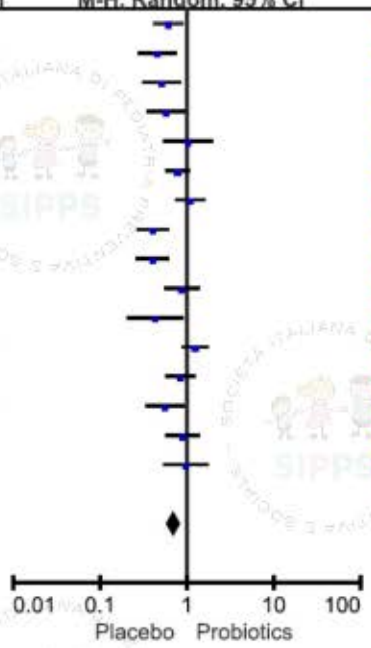
W. Jiang et al. Pediatric Drugs 2020

Forest plot for pooled relative risk ratio of AD in those treated with probiotics

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dotterud 2010	29	138	48	140	7.0%	0.61 [0.41, 0.91]
Gao 2004	16	74	35	74	6.0%	0.46 [0.28, 0.75]
Kalliomaki 2001	15	64	31	68	5.8%	0.51 [0.31, 0.86]
Kim 2010	12	33	22	35	5.8%	0.58 [0.34, 0.97]
Kopp 2008	14	50	12	44	4.6%	1.03 [0.53, 1.98]
Niers 2009	27	50	33	48	7.9%	0.79 [0.57, 1.08]
Plummer 2019	35	118	37	137	7.1%	1.10 [0.74, 1.62]
Rautava a 2012	21	73	22	31	6.7%	0.41 [0.26, 0.62]
Rautava b 2012	20	70	22	31	6.6%	0.40 [0.26, 0.62]
Soh 2009	27	124	30	121	6.4%	0.88 [0.56, 1.39]
Stephen 2014	9	171	21	173	3.9%	0.43 [0.20, 0.92]
Taylor 2007	43	88	34	87	7.7%	1.25 [0.89, 1.75]
Wickens 2018	37	203	43	200	7.1%	0.85 [0.57, 1.26]
Wickens a 2008	24	157	22	80	5.8%	0.56 [0.33, 0.93]
Wickens b 2008	39	158	22	80	6.5%	0.90 [0.57, 1.40]
Yang 2012	16	65	16	64	5.1%	0.98 [0.54, 1.80]
Total (95% CI)		**1636**		**1413**	**100.0%**	**0.70 [0.57, 0.84]**
Total events	384		450			

Heterogeneity: Tau² = 0.10; Chi² = 42.32, df = 15 (P = 0.0002); I² = 65%

Test for overall effect: Z = 3.70 (P = 0.0002)



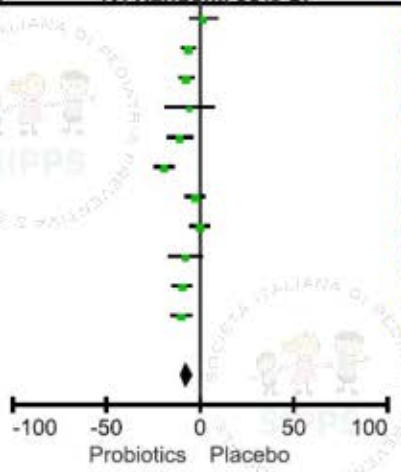
W. Jiang et al. Pediatric Drugs 2020

Forest plot for WMD in change in SCORAD values in those treated with probiotics

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Folster-Holst 2006	-8	13.8	26	-9.8	14.3	27	8.0%	1.80 [-5.77, 9.37]
Gerasimov 2010	-14.2	9.9	43	-7.8	7.7	47	11.6%	-6.40 [-10.09, -2.71]
Han 2012	-9.1	10.6	58	-1.8	12.1	60	11.2%	-7.30 [-11.40, -3.20]
Komei 2019	-8.1	18.5	25	-2.5	25.6	20	4.3%	-5.60 [-18.96, 7.76]
Lue 2017	-23.2	15.2	30	-12.4	12.8	32	8.5%	-10.80 [-17.82, -3.78]
Vicente 2018	-27	9.6	23	-7.8	9.8	24	9.9%	-19.20 [-24.75, -13.65]
Viljanen a 2005	-22.9	16.1	80	-20.3	12.6	37	10.0%	-2.60 [-7.98, 2.78]
Viljanen b 2005	-20.4	15.8	76	-20.3	12.6	37	10.0%	-0.10 [-5.49, 5.29]
Weston 2005	-18.2	14.6	28	-10.2	19.7	28	6.8%	-8.00 [-17.08, 1.08]
Woo 2010	-13.8	12	41	-4.2	11.8	34	10.0%	-9.60 [-15.01, -4.19]
Yesilova 2012	-23	11.6	20	-12.8	5.7	20	9.7%	-10.20 [-15.86, -4.54]
Total (95% CI)			**450**			**366**	**100.0%**	**-7.23 [-10.59, -3.88]**

Heterogeneity: Tau² = 21.69; Chi² = 35.99, df = 10 (P < 0.0001); I² = 72%

Test for overall effect: Z = 4.23 (P < 0.0001)



W. Jiang et al. Pediatric Drugs 2020

Comparative effectiveness of probiotic strains for the treatment of pediatric atopic dermatitis: A systematic review and network meta-analysis TAN-LIM ET AL. *Pediatr Allergy Immunol.* 2020

Efficacy Outcome vs Placebo

CoE Assessment

Mix1

Bifidobac

High quality

7347

Mi

Bifidobact

ality

alivarius

Mi

ality

Lactobacillus fermentum GM090 + *Lactobacillus paracasei* GMNL-133i

Lactobacillus casei DN-114001

Moderate quality

Among the six mixed probiotic preparations, three (Mix1, Mix4, and Mix6) showed benefit in reducing atopic dermatitis symptoms compared with placebo. This is suggestive of the synergistic effects of certain probiotic strains. The therapeutic benefits of these mixed preparations may be due to better simulation of the normal diversity of the human microbiome.

Comparative effectiveness of probiotic strains for the treatment of pediatric atopic dermatitis: A systematic review and network meta-analysis TAN-LIM ET AL.

Pediatr Allergy Immunol. 2020

Due to the strain-specific effect of probiotics and mixed preparations, it is difficult to recommend probiotics as a general class of drugs for treatment of pediatric atopic dermatitis. However, specific probiotic strains and mixed preparations may provide benefit for pediatric patients with atopic dermatitis to relieve allergic symptoms.

Study	Country
Fölster-Holst 2006[23]	Germany
Gøbel 2010[24]	Denmark
Gore 2012[25]	United Kingdom
Grüber 2007[27]	Germany
Han 2012[27]	Korea
Isolauri 2000[28]	Finland
Klewicka 2011[29]	Poland
Lin 2015[44]	China
Miniello 2010[30]	Italy
Navarro-López 2018[31]	Spain
Nermes 2011[32]	Finland
Prakoeswa 2017[33]	Indonesia
Rosenfeldt 2003[34]	Denmark
Sistek 2006[35]	New Zealand
Torii 2011[36]	Japan
Wang 2015[27]	Taiwan
Weston 2005[38]	Australia
Woo 2010[39]	Korea
Wu 2017[40]	Taiwan
Yan 2019[43]	Taiwan
Yang 2014[41]	Korea
Yesilova 2012[42]	Turkey

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk of bias (efficacy outcome)	Overall risk of bias (safety outcome)
Fölster-Holst 2006	+	?	+	+	+	+	+	?	?
Gore 2012	+	+	+	+	+	+	+	+	+
Grüber 2007	+	+	+	+	+	+	+	+	+
Gøbel 2010	+	?	+	+	+	+	+	?	?
Han 2012	+	+	+	+	+	+	+	+	+
Isolauri 2000	+	?	+	+	+	+	+	?	?
Klewicka 2011	+	?	+	+	?	+	+	?	?
Lin 2015	+	?	?	?	?	+	+	?	?
Miniello 2010	+	+	+	+	+	+	+	+	+
Navarro-López 2018	+	+	+	+	+	+	+	+	+
Nermes 2011	+	?	+	+	+	+	+	?	?
Prakoeswa 2017	+	?	+	+	+	+	+	?	?
Rosenfeldt 2003	+	?	+	+	+	+	+	?	?
Sistek 2006	+	+	+	+	+	+	+	+	+
Torii 2011	+	+	+	+	-	+	+	-	-
Wang 2015	+	+	+	+	+	+	+	+	+
Weston 2005	+	+	+	+	+	+	+	+	+
Woo 2010	+	?	+	+	+	+	+	?	?
Wu 2017	+	?	+	+	+	+	+	?	?
Yan 2019	+	?	+	?	-	+	+	-	-
Yang 2014	+	+	+	+	-	+	+	-	-
Yesilova 2012	+	+	+	+	+	+	+	+	+

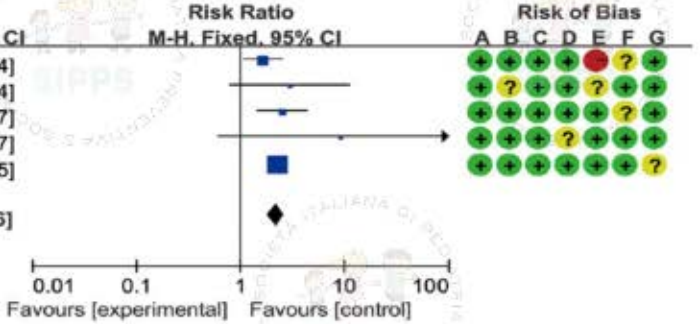
Lactobacillus rhamnosus GG for Cow's Milk Allergy in Children: A Systematic Review and Meta-Analysis

frontiers in Pediatrics

Study or Subgroup	LGG group Events	Total	Placebo group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
A.Basturk,2019	29	51	19	55	25.6%	1.65 [1.07, 2.54]
L.Paparo,2019	6	10	2	10	2.8%	3.00 [0.79, 11.44]
R.Berni Canani,2012	22	27	9	28	12.4%	2.53 [1.44, 4.47]
R.Berni Canani,2015	7	12	0	7	0.9%	9.23 [0.61, 140.67]
RN.Rita Nocerino,2021	59	73	104	292	58.3%	2.27 [1.88, 2.75]
Total (95% CI)		**173**		**392**	**100.0%**	**2.22 [1.86, 2.66]**
Total events	123		134			

Heterogeneity: $Chi^2 = 3.32$, $df = 4$ ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: $Z = 8.80$ ($P < 0.00001$)



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Significant differences between the tolerance rate of the LGG and control groups were observed overall, and the results showed that LGG was more able to gain immune tolerance (RR, 2.22; 95% CI, 1.86–2.66). Meanwhile, no obvious heterogeneity was found in these five trials ($I^2 = 0.0\%$, $p < 0.00001$).

CONCLUSION

Our results indicated that LGG may have moderate-quality evidence to promote oral tolerance in children with CMA, and it may have a role in promoting the recovery of intestinal symptoms. However, this conclusion must be treated with caution due to the small number of included studies. Although this result shows that the management of children with CMA has a positive trend, more powerful RCTs with standardized measurements are needed to evaluate the most effective dose and treatment time for children with CMA and fully understand its potential adverse reactions.

Gut microbiota biomodulators, when the stork comes by the scalpel

Vito Leonardo Miniello *, Angela Colasanto, Fernanda Cristofori, Lucia Diaferio, Laura Ficele, Valentina Santoiemma, Ruggiero Francavilla

Modalità del parto

Modalità allattamento

Antibiotici Ferro PPI

Miniello et al 2017

"Prega per noi adesso
e nell'ora della nostra nascita"
Thomas Stearns Eliot