LE GIORNATE DELLA SALUTE E DEL BENESSERE :
INNOVAZIONE E RICERCA
Milano 30 Giugno-1 Luglio 2016

Modulazione dell'omeostasi intestinale

Dr.ssa Barbara Aghina , Molecular Biologist
Nutraceutical s and Medical Devices Project Leader
Scientific Manager ECM Order Pharmacists Brescia
Scientific board memeber

Intestine* = MICROCOSM P.N.E.I., *i.e. main organ for homeostatic control.

P
N
E
I

Tutte le malattie hanno origine nell'intestino.

Ippocrate (460 a.C.-377 a.C.)

✓**PROCESSING AND ABSORPTION OF NUTRIENTS AND DETOXIFICATION SYSTEM**

✓**NEUROPEPTIDES:**
serotonin, tryptophan, substance P

✓**NEUROHORMONES and HORMONES:**
somatostatin, enkephalins, gastrin, bombesin, histamine, neurotensin, secretin, motilin, enteroglucagon, cholecystokinin, gip (gastric inhibitory polypeptide).
Some of them act as non-noradrenergic and non-cholinergic neurotransmitters (NANC).

CYTOKINES

✓**GALT SYSTEM**

LOW-GRADE CHRONIC INFLAMMATION: DRIVER OF AGEING = MOTHER OF ALL DISEASES

- C.A.D. (Coronary Artery Disease)
- C.V.D. (Cardiovascular Disease)
- ATHEROSCLEROSIS
- …

CARDIO-VASCULAR SYSTEM

•OSTEOARTHRITIS
•OSTEOPOROSIS…
- …

MUSCULO-SKELETAL SYSTEM

INTESTINE

•IBDs/IBS (Inflammatory Bowel Disease/Inflammatory Bowel Syndrome)
•GLUTEN SENSITIVITY
•CELIAC DISEASE
•LEAKY GUT SYNDROME…

•IMPOTENCE
•PCOS (Polycystic Ovary Syndrome)

REPRODUCTIVE SYSTEM

LOW GRADE CHRONIC INFLAMMATION

C.N.S.

- DEPRESSION
- ALZHEIMER'S DISEASE
- AUTISM
- NEURODEGENERATIVE DISEASES
- …

•UV DAMAGE
•SKIN AGEING
•….

EPITHELIAL TISSUES

IMMUNE SYSTEM

- CANCER
- AUTOIMMUNE DISEASES
- C.F.S. (Chronic Fatigue Syndrome)
- …

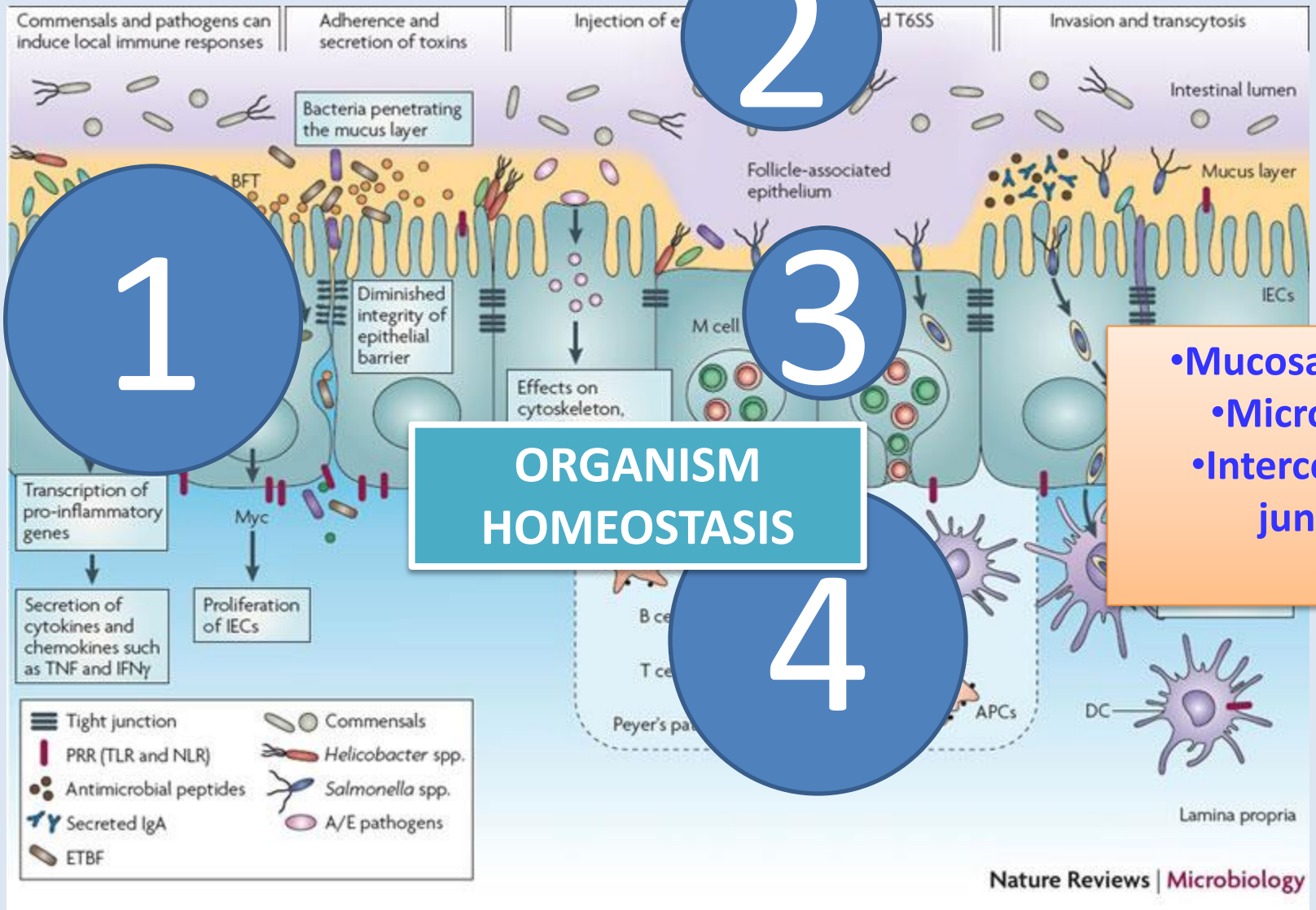
ENDOCRINE-METABOLIC SYSTEM

- OBESITY
- TYPE II DIABETES
- METABOLIC SYNDROME
- …

Controlling *low grade chronic inflammation* means:

1. **primarily prevent** chronic-degenerative diseases
1 counteract ***ageing***
2 support **wellness**

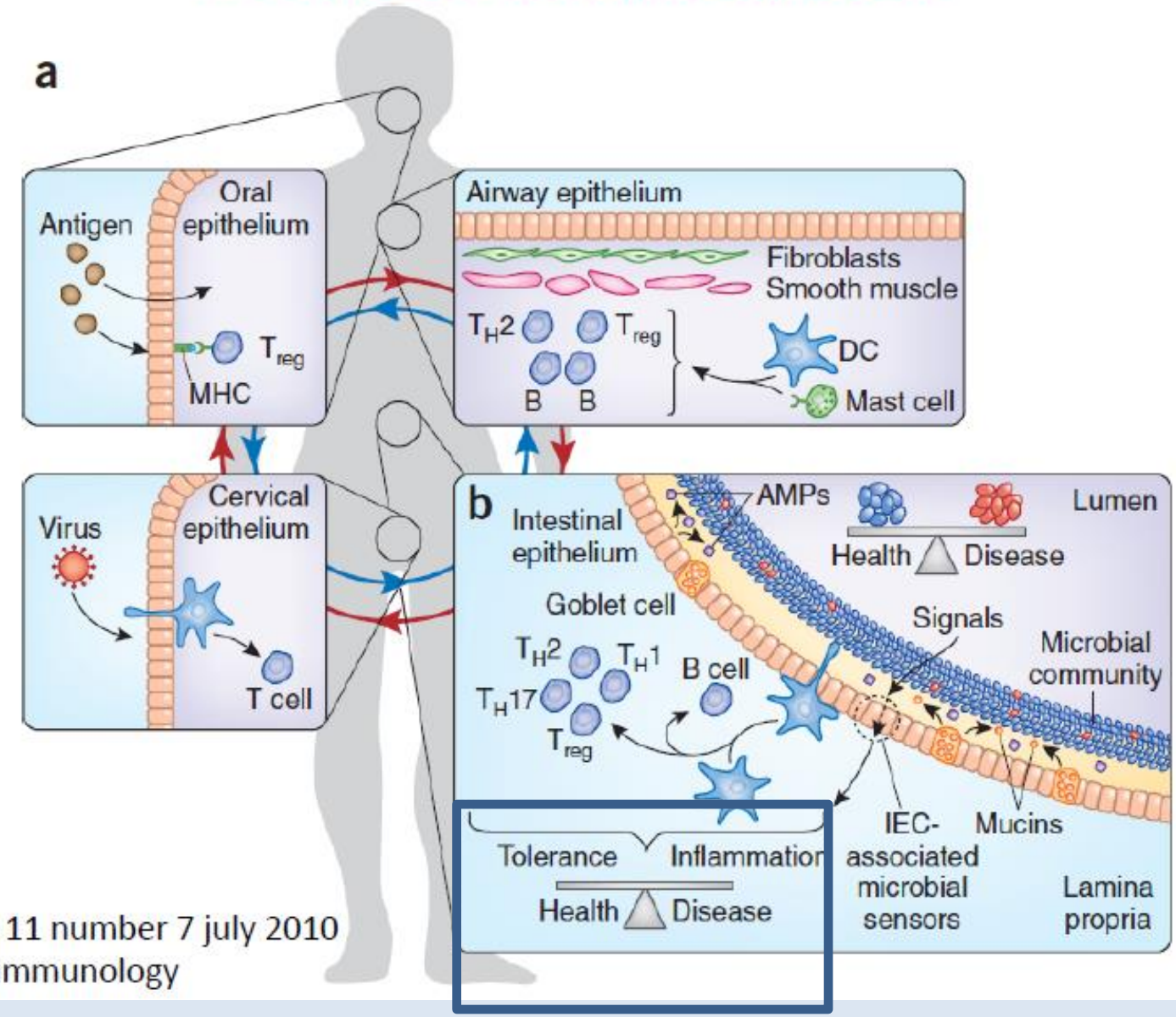
GUT "HEALTH HUB"



- Mucosa layer
- Microbiota
- Intercellular junctions
- GALT

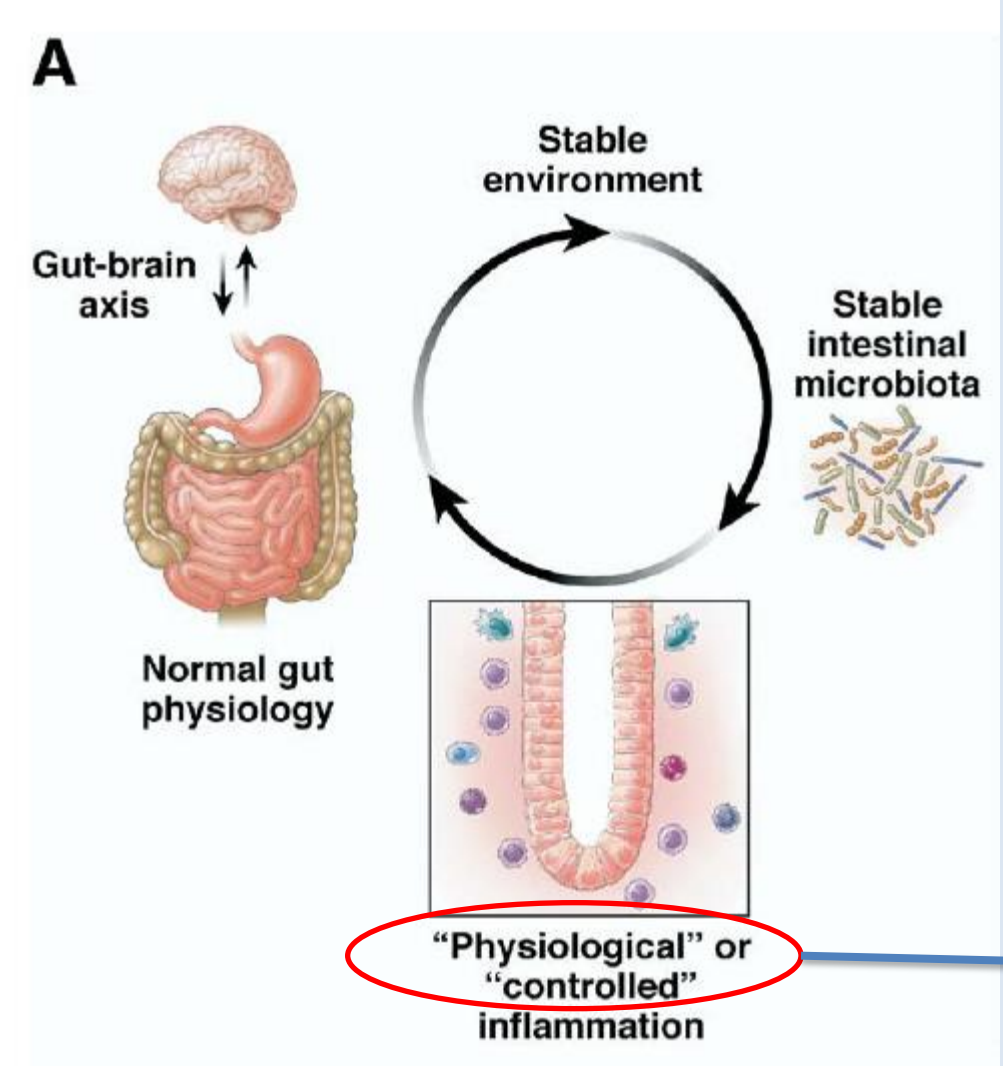
Nell S. et al. The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models.
Nature Reviews Microbiology 2010

Il futuro dell'immunità mucosale



volume 11 number 7 july 2010
nature immunology

Influence of GI Physiology on the Microbiota



In normal conditions, the GI tract provides a stable habitat for commensal bacteria, which support its structural and functional integrity even through a physiological controlled inflammation

e.g. immune tolerance

Collins S M, Bercik P. The Relationship Between Intestinal Microbiota and the Central Nervous System in Normal Gastrointestinal Function and Disease. GASTROENTEROLOGY 2009;136:2003–2014

Physiological Nutraceuticals is the most modern and innovative expression of Nutritional science AND FOOD SUPPLEMENTATION .

It is based on the principles of **Human Physiology** and on the concept that food, nutrients and food supplements are the main and essential “therapeutic” tools for:

- **restoring the original physiological functions in a sick body;**
- **preventing the onset of pathological conditions;**
- **counteracting the aging process, by acting on the mechanisms of homeostatic regulation.**

15 years to…

…define an entirely original and innovative method…

and…

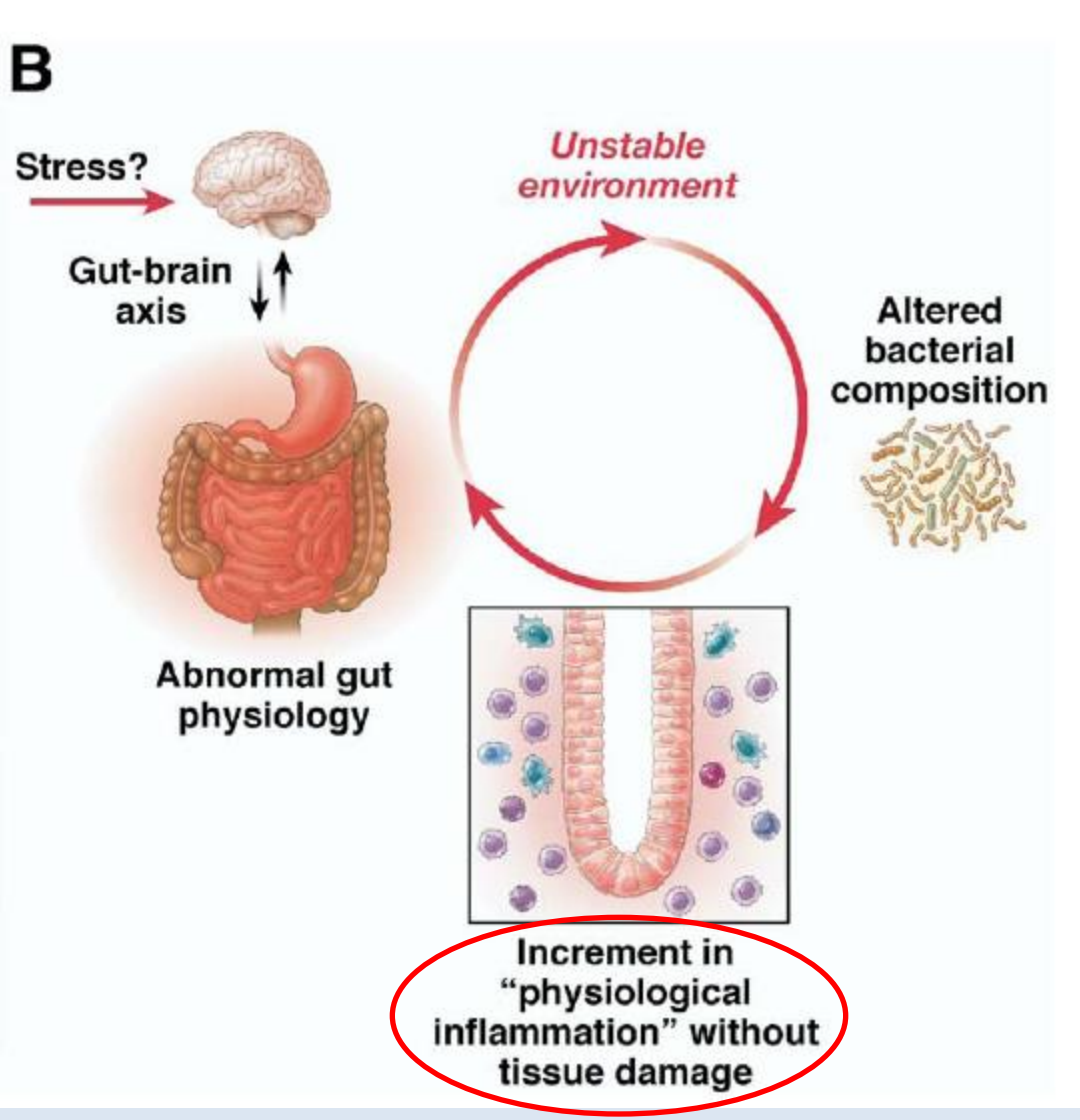
…help to create a new concept in the field of Nutraceuticals.

P N E I

ABSORPTION OF NUTRIENTS HOMEOSTASIS

PROJECT OF BASIC AND CLINICAL RESEARCH

Influence of GI Physiology on the Microbiota



An alteration of the **GI physiology produces** an altered habitat, which in its turn, supports a different microbiota.
This could represent the basis for maintaining a **GI malfunction after the Microbiota disturbance**; this could also explain the development and persistence of dysbiosis in the event of a primitive alteration of the GI physiology.

MICROBIOTA

- **Inflammation *Controller***
- ***GUT Axis* Function *Controller***

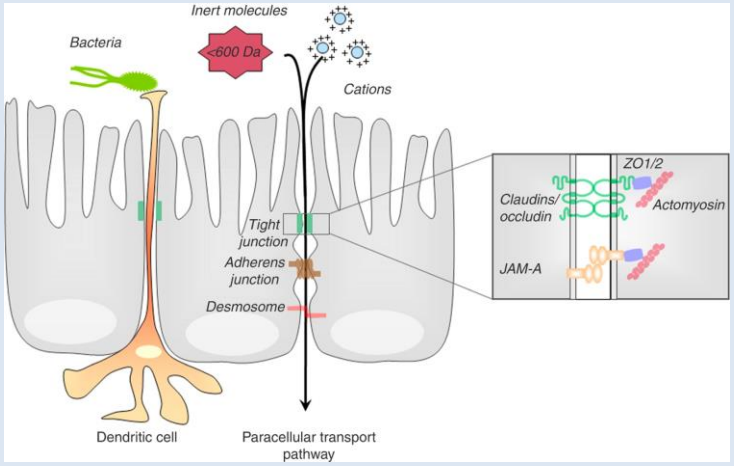
Collins S M, Bercik P. The Relationship Between Intestinal Microbiota and the Central Nervous System in Normal Gastrointestinal Function and Disease. GASTROENTEROLOGY 2009;136:2003–2014

Physiological Nutraceuticals : sistemi giunzionali mucosa intestinale

These pathological conditions, which are also due to a loss of intestinal homeostasis, lead to a significant modification of the intestinal barrier and in particular **the opening of Tight Junctions (TJ) of apical epithelial cells**

✓The alteration of the junctional systems**, compared to an inflammatory event**, results in the damage of the mucosal layer with modification of the typical morphology of the intestinal epithelium in terms of shape and structure of the epithelium itself (size and distribution of the villi) and tissue cellular composition (alteration of the numerical relationships among the cell types normally present);

✓the activation of the immune response makes it possible to find also cells of the immune system in the gut epithelium in the form of inflammatory infiltration



S Ménard, N Multiple facets of intestinal permeability and epithelial handling of dietary antigens. Mucosal Immunology 2010

FOOD AND CHRONIC INFLAMMATORY DISEASES

croniche

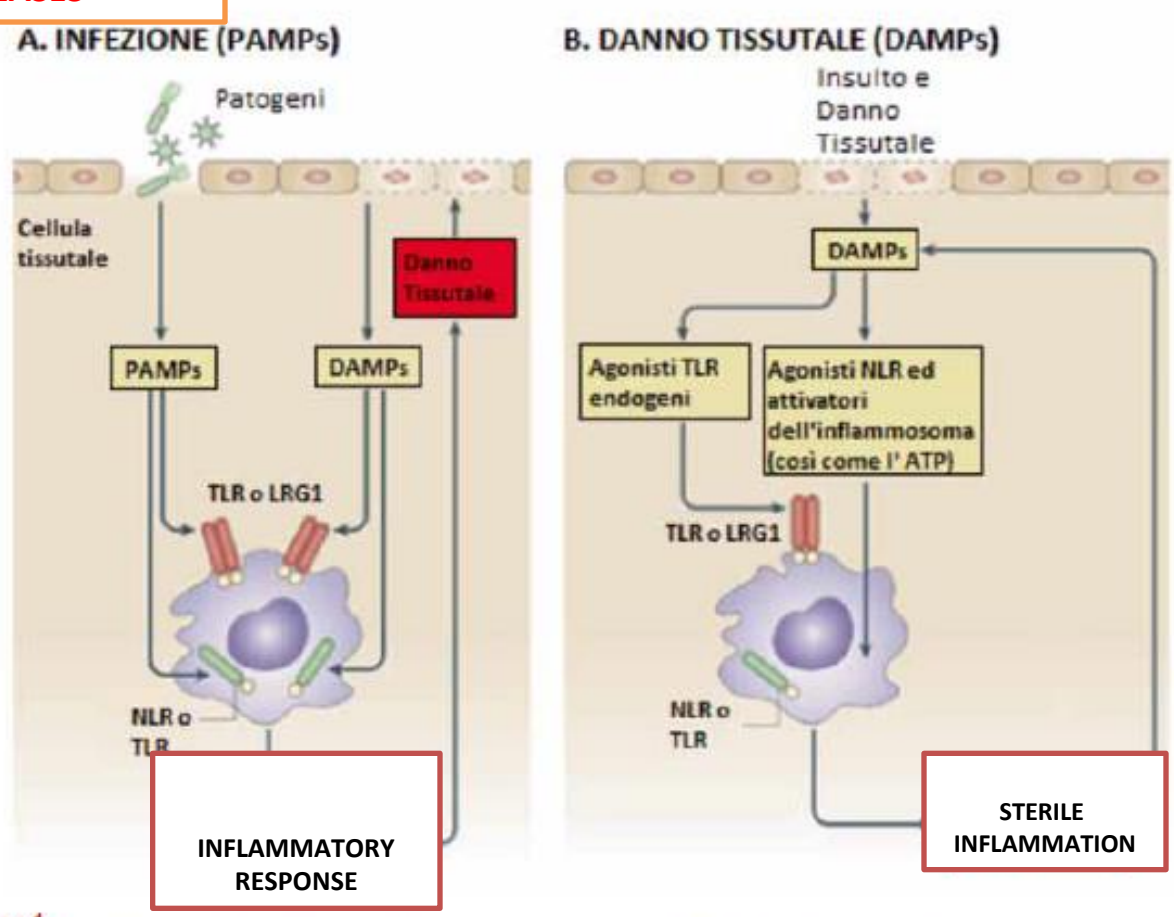
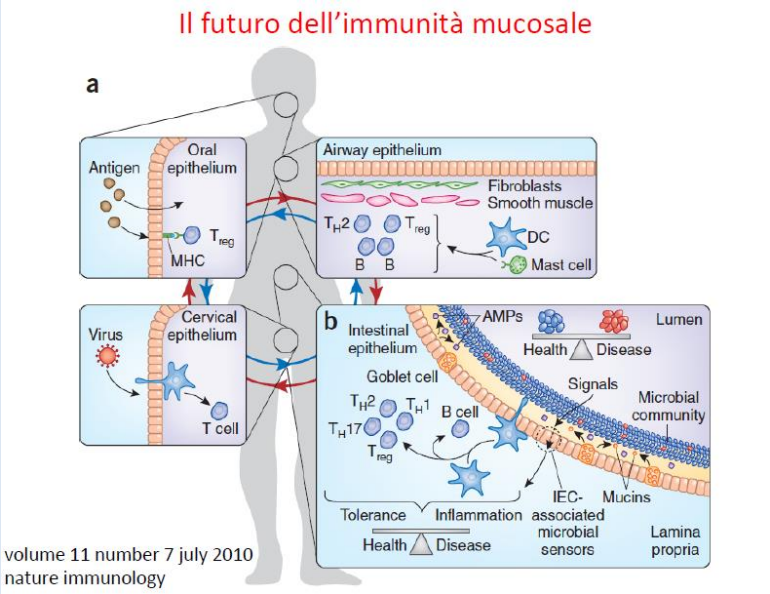


Figura 1.
Sono rappresentati due modelli per l'attivazione della risposta immune regolata da PRRs *(Pattern-Regognition Receptors)*.
A) Modello molecolare della risposta immune alle infezioni regolata dai PAMPs *(Pathogen Associated Molecular Patterns)*, che possono essere ligandi per il recettore Toll-like (TLR), il recettore NOD-like (NLR) e il Leucine rich alpha-2-glycoprotein 1 (LRG1). L'attivazione di questi recettori porta alla produzione di citochine pro-infiammatorie con conseguente risposta infiammatoria e danno tissutale che porta al rilascio di DAMPs *(Damage Associated Molecular Patterns)* – che agiscono sinergicamente con i PAMPs per indurre la riposta infiammatoria.
B) Modello molecolare della risposta immune al danno tissutale regolata dai DAMPs – che agiscono da ligandi per i recettori: TLR, NLR e LRG1 avviando una risposta infiammatoria, così detta sterile, che porta al danno tissutale.

Physiological Nutraceuticals

"3Rs" Treatment
CENTRAL ROLE OF THE INTESTINE

REMOVE TOXINS FROM THE DIGESTIVE TRACT

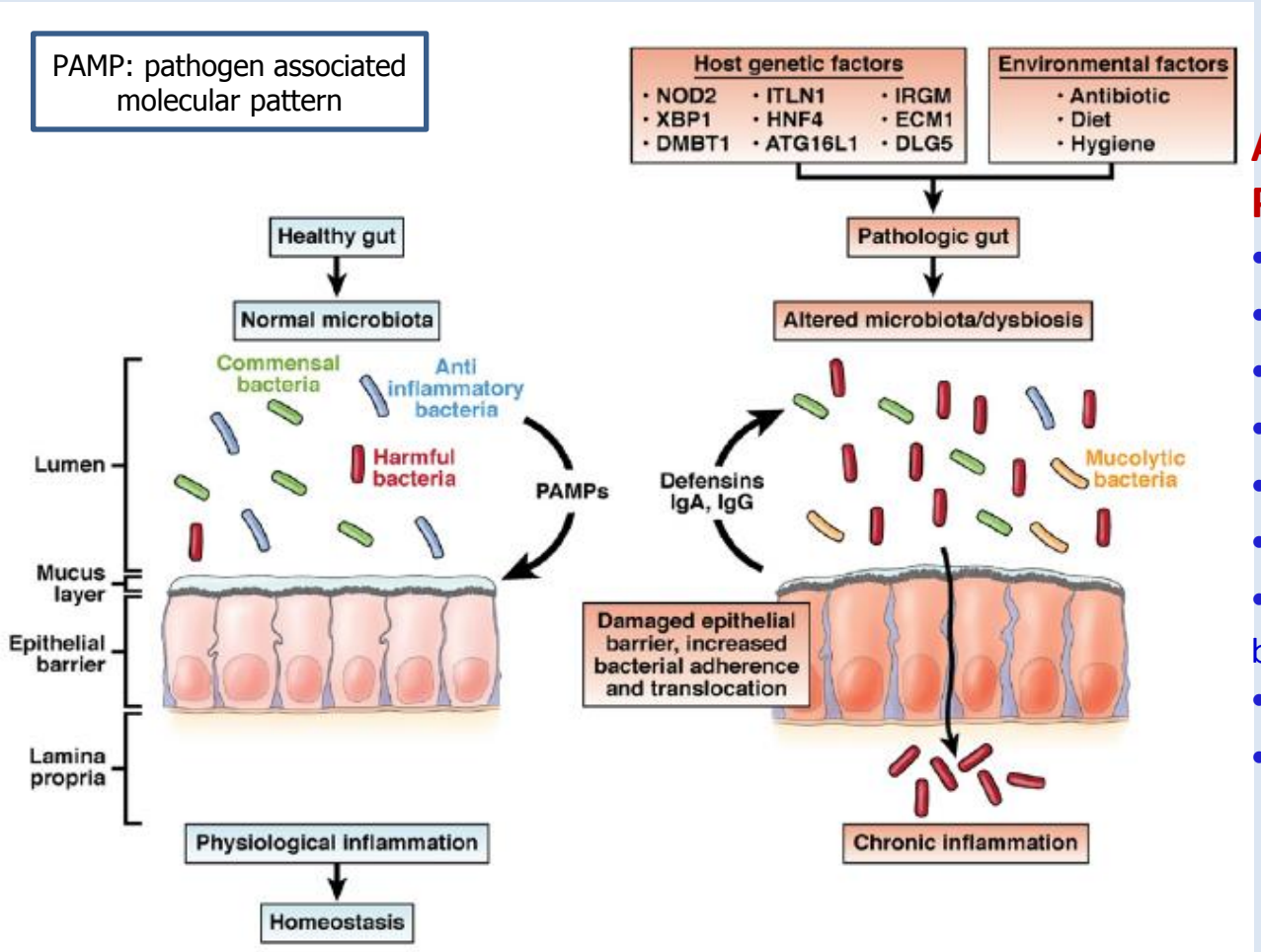


REPLACE THE MICROBIOTA

REPAIR
THE GASTRO-INTESTINAL MUCOSA

REMOVE

The microbiota and host genetic and environmental factors contribute to pathogenesis of IBDs



ALTERED INTESTINAL PERMEABILITY:

- Celiac disease;malnutrition
- IBS; CHRON ; Ulceratice colitis
- Pancreatic insufficiency
- Dermatological diseases
- Liver disease
- High levels of ROS species
- SIBO syndrome of excessicve growth of bacteria in the small intestine
- Candida Overgrowth Syndrome
- Contamination with mycotoxins

Chassaing B, Darfeuille-Michaud A. The Commensal Microbiota and Enteropathogens in the Pathogenesis of Inflammatory Bowel Diseases. GASTROENTEROLOGY 2011;140:1720–1728

REMOVE

Wash out of the digestive tract

- The *Functional System of Detoxification* (FSD) includes the lungs, the liver, the intestine, the kidneys and other organs responsible for the dilution and mobilization of toxins, of their biotransformation and elimination

- An acute impact of endogenous toxins always brings about a specific response by organs and systems: acute endotoxicosis

- The development of endotoxicosis is associated with failure of the FSD, to a general impairment of blood rheology and to alterations of the responsiveness of the immune system, which needs to maintain and replace the impaired elements of the FSD through an active detoxification

nutrimi
VIII Forum Internazionale di Nutrizione Pratica
SOTTO L'ALTO PATRONATO DEL PRESIDENTE DELLA REPUBBLICA

CASE STUDY
Selective wash-out of the digestive tract: mechanism of action and new applications

Dr. Barbara Aghina, Biologist
Specialized in Cellular and Molecular Biology

Detoxifying potential and clinical efficacy of the enterosorbent *polymethylsiloxane polyhydrate* used in combined treatment for different diseases in children and adults

N.V. Nagornaya, A.V. Dubovaya
University of Medicine Donetsk under the nema of M. Gorky, Ukraine

REMOVE

Wash out" of the digestive tract

Enteroadsorption

Therapeutic method, based on the ability of the **Enteroadsorbent,** for the purpose of physiological excretion

to bind and capture:

- different chemical and microbiological toxic susbstances (xenobiotics)
- intermediate and final metabolites

which can intoxicate and alter the environment and the gastrointestinal function and therefore the body health

Detoxifying potential and clinical efficacy of the enterosorbent *polymethylsiloxane polyhydrate* used in combined treatment for different diseases in children and adults

N.V. Nagornaya, A.V. Dubovaya
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REMOVE

Wash out of the digestive tract

The amount of toxic susbstances which penetrate the body through the intestinal lumen depends on the conditions of its parietal mucosa (integrity or non-integrity of the "mucosal barrier").

The success and the safety of the treatment with an enteroadsorbent therefore depend on the interaction between the product used and the substance adsorbed by respecting the physiology and morphology of the intestinal mucosa:

SELECTIVE ENTEROADSORPTION

Research Institute of Clinical and Experimental Lymphology SB RAMS, Novosibirsk;

Further to a recent European legislation, the **Circular letter of 27/1/2014, issued by** the Italian Ministry of Health states **that, starting from the production batches of 01/02/2014, the use of some substances such as:**

Sodium and Aluminium silicate (E554), Potassium and Aluminium Silicate (E555), Calcium and Aluminium Silicate (E556), Bentonite (E558), Aluminium or Kaolin Silicate (E559),

is forbidden due to their aluminium content. Among these substances, there are some clays that are normally used in the formula of some dietary supplements;

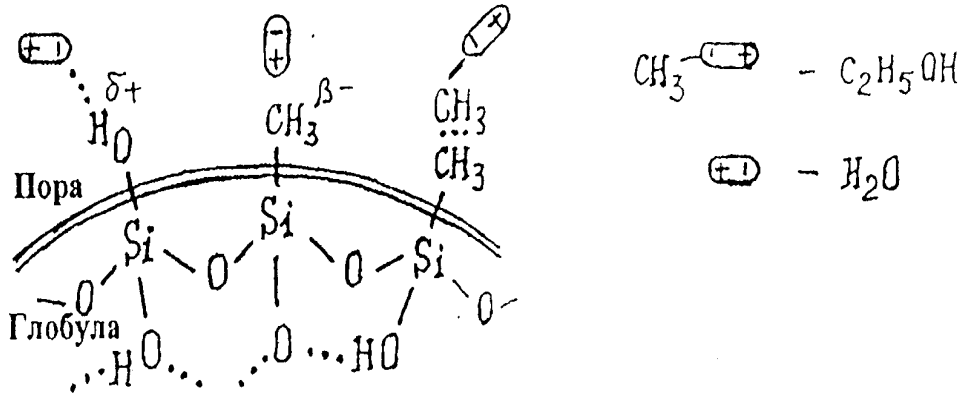
Concerning other clays, the type, the content and the amount that can be taken, must be shown in the label. This notification must be accompanied by a certificate stating the aluminium content.

This prohibition or revision of the label statements regarding safety basically involves the **main food supplements made from clay (bentonite, zeolite, kaolin) Polymethylsiloxane polyhydrate is not included in the category forbidden by the a.m. legislation from a regulatory point of view or due to its active ingredient (Polymethylsiloxane polyhydrate) as it does not contain Aluminium.**

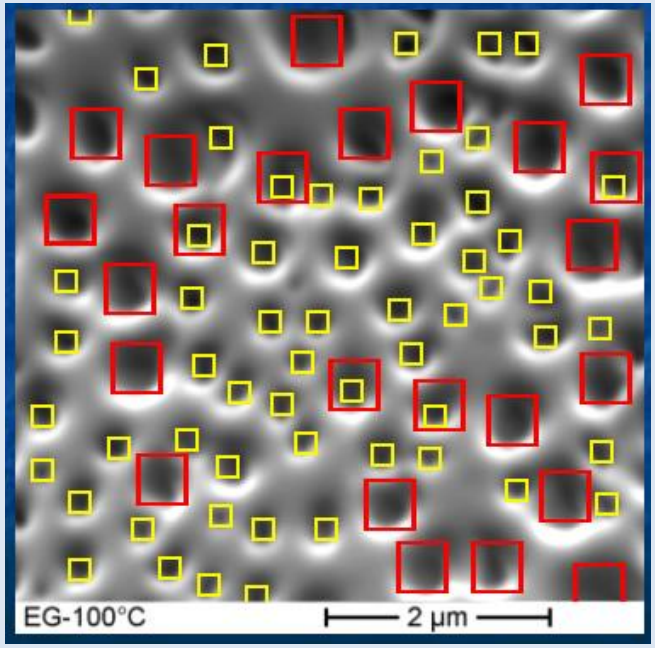
Hydrogel of methyl silicic acid **in aqueous phase for oral use**

CE MEDICAL DEVICE

Polymethylsiloxane polyhydrate



Globular structure of polymethylsiloxane polyhydrate.
The structure is confirmed in electronic and microscopic way (1): the globules sized from 7 to 15 nm are distinctly fixed. The shown globules structure and sorbent surface
are determined according to the thermal analysis data, IK, ESP, 1N- and 29Si-YaMR- spectral analysis, study of non-elastic neutron spread spectrum, as well as carrying out quantum-chemical modelling.
REGULATIONS FOR CE MEDICAL DEVICES



Pore of *pollymethylsiloxane polyhydrate.* of 200 nm

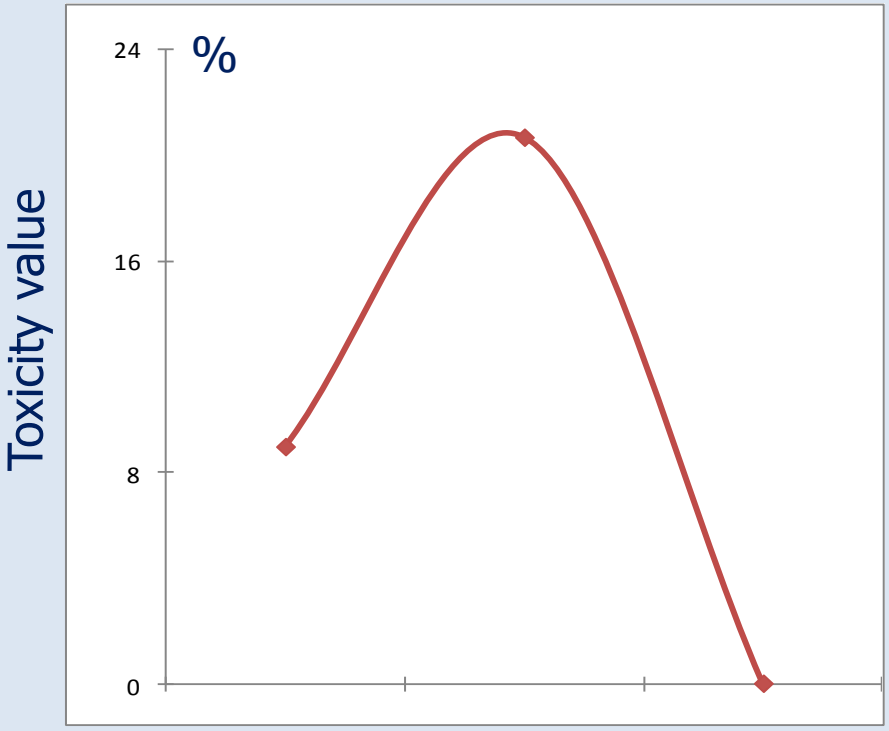
Pore of *pollymethylsiloxane polyhydrate.* of 400 nm

Electron microscope image (x20000)

ITS SELECTIVE ADSORBENT PROPERTY FOR ENDOGENOUS OR EXOGENOUS TOXIC AGENTS IS 2.5 TIMES HIGHER(1) THAN THAT OF THE OTHER ENTEROADSORBENTS KNOWN

(1) Fonte : Bioline.

Adsorbing and detoxifying properties of *polymethylsiloxane polyhydrate*



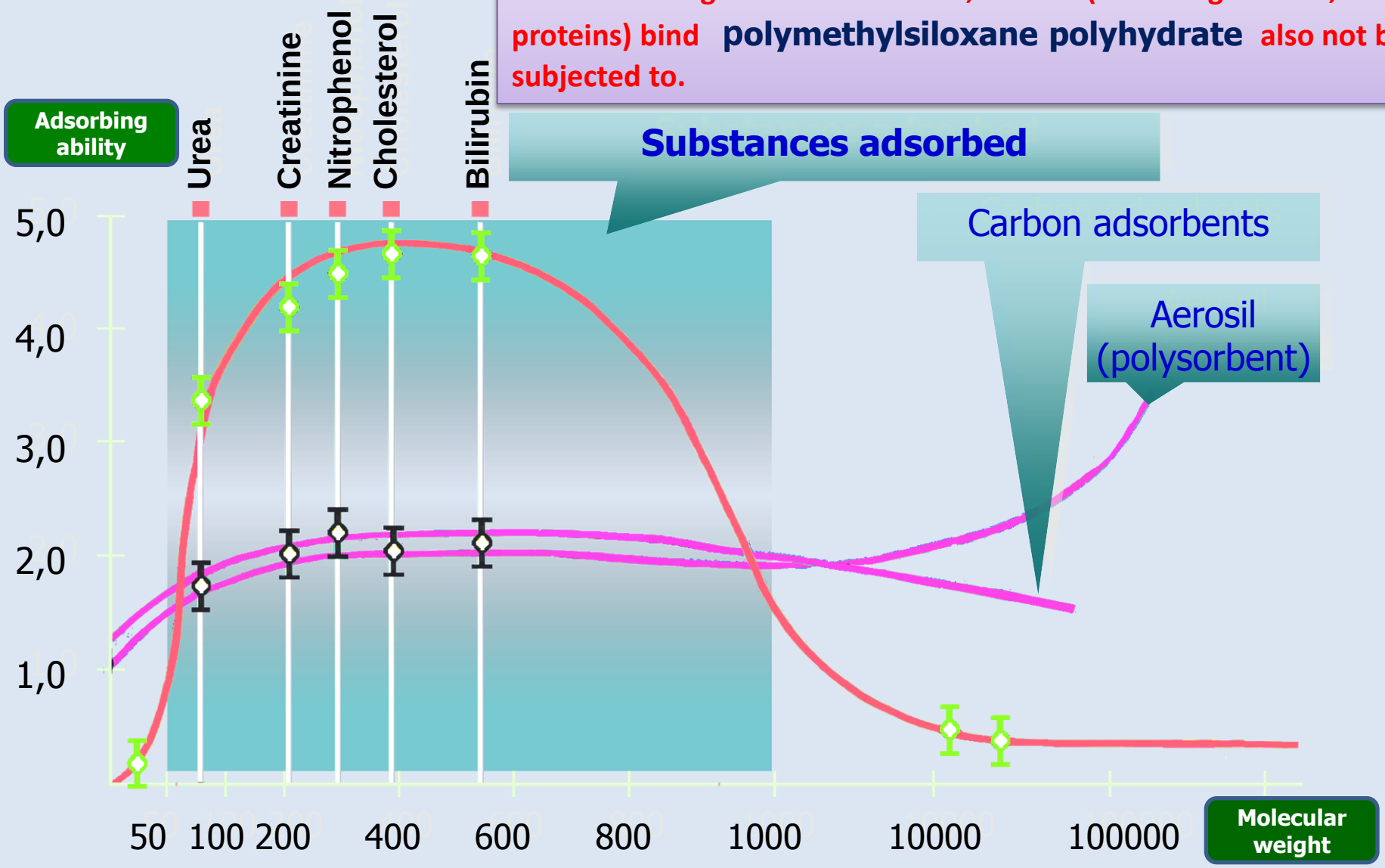
After being ingested, it forms a special three-dimensional network structure capable of selectively capturing endogenous or exogenous toxic substances of various origin, removing them from the intestine WITHOUT ALTERING THE MUCOSAL BALANCE

Odorless, tasteless, colorless, inert, gluten-, lactose-, glucose-, protein-, preservative-, flavoring-, additive-free

From: Bioline

This shows its selective property and better capture ability compared to normal enteroadsorbents

It almost does not bind substances with molecular weight less than 60-70 (metal ions, mineral salts, electrolytes). Substances with a molecular weight of more than 10,000 AU (immunoglobulins, proteins) bind **polymethylsiloxane polyhydrate** also not be subjected to.



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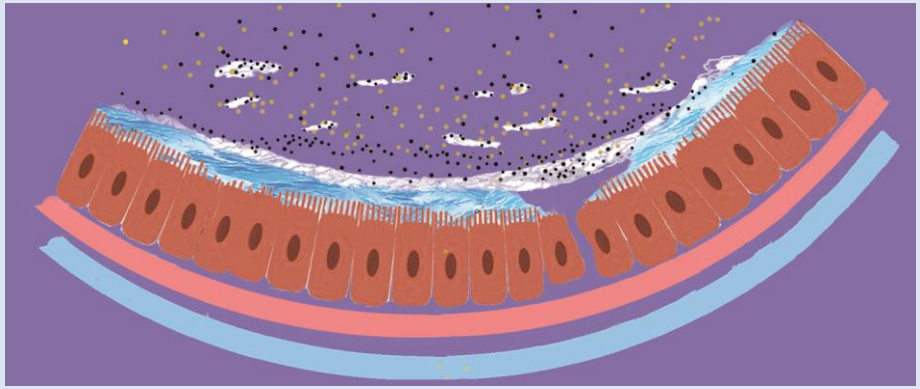


Polymethylsiloxane polyhydrate FORMS A **TEMPORARY** AQUEOUS PHASE GEL WHICH **DOES NOT CROSS** THE MUCOSAL BARRIER EVEN IN THE EVENT OF LEAKY GUT SYNDROME AND **DOES NOT ADHERE** TO THE GASTRO-INTESTINAL MUCOSA . It is eliminated within 12 hours. From: Bioline

Elimination intestinal adsorbents (enterosorbents) therapy in children with asthma living in poor sanitary conditions

Federal research centre of medical technologies of risk management to the health of the population, Perm, Russia
Zaitseva N., Ustinova O.

- According to recent epidemiological and toxicological data, children who live in poor sanitary conditions show impaired physical development, including morphological abnormalities and chronic diseases of the central nervous system and the respiratory, cardiovascular, musculoskeletal, endocrine and digestive Systems.

- Among the industrial substances, an important role is represented by metals, which accumulate in the tissues and organs. Toxic effects are due to the type of metal, its concentration, along with concurrent pathological factors and overall health (immune responsiveness, sensitivity, etc.).

- The study was conducted on 236 children suffering from mild asthma (experimental Group) living in areas close to metallurgical plants, where the values of composition of the air, considering the percentage of Manganese, Chromium, Lead and Nickel, exceeded the upper limits allowed.

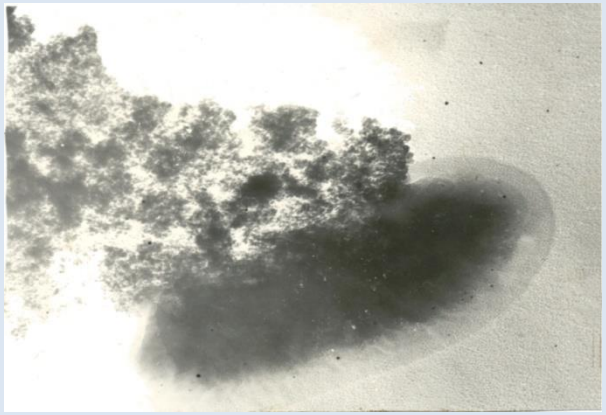
- The control Group, homogeneous for age, gender and residential area, consisted of 41 children.

- For therapeutic purposes, for the reduction of blood concentrations of toxic metals considered, the polymethylsiloxane polyhydrate for 2 consecutive weeks of therapy was tested:

- The data show that the use of *polymethylsiloxane polyhydrate* allows to obtain a significant reduction in the amount of Cr and Ni (56-66%) and of Mn and Pb (12-24%) compared to the controls within 2 consecutive weeks of therapy

SELECTIVE interactions of polymethylsiloxane polyhydrate with pathogenic microflora

Microbiology department KMAPE. Property of Grigoriev A.V.



Salmonella tiphimurium interacts with polymethylsiloxane polyhydrate ; polymethylsiloxane polyhydrate penetrates through the lipopolysaccharide layer causing damage to the cellular membrane of bacteria

Develops a high selective adsorbing ability and is capable of eliminating pathogenic microorganisms such as:

- ***Helicobacter pylori,***
- ***Salmonella, Shigella, Klebsiella, Escherichia coli (Enterohaemorrhagic E.coli EHEC)***
- **Gram(–) e Gram(+) bacteria (Clostridium genus)**
- **Rotavirus**
- **fungi such as *Candida albicans;***

polymethylsiloxane polyhydrate

Helps to restore the microbiota (Lactobacilli and Bifidobacteria)

Reducing the symptoms of dysbiosis, and selectively acting on the pathogenic microflora.

the endogenous bacteria have specialized bonds (adhesins) that serve to tightly bind specific receptors located in the epithelium (complementarity) with a ligand-receptor mechanism of adhesion to the intestinal mucosa.

"A strong reduction of the Clostridia capacity has been hard, the diarrhea remission time has improved"

Dr Federico Meyer Head of the Neurological Rehabilitation Dept. of Ulivella e Glicini Clinic, Florence, 2015

MORPHOFUNCTIONAL CHARACTERISTICS OF MUCOSAL LAMELLA UNDER DIFFERENT METHODS OF ULCER TREATMENT

Research Institute of Clinical and Experimental Lymphology Novosibirk 2002

First group (control group) – 30 patients with ulcer treated with standard therapy according to P. Grigoriev (1995), which includes: H2-blockers + antibacterial (eradicational) therapy + antacids + motility regulators.

Second group – 30 patients, standard treatment + **polymethylsiloxane polyhydrate** as eradication treatment.

Doxycycline was adiministered together with polymethylsiloxane polyhydrate at the same time: 0.3 grams of doxycycline were added to 15 grams of sorbent in an aqueous medium. The mixture was taken once a day after morning meal over 10 day period.

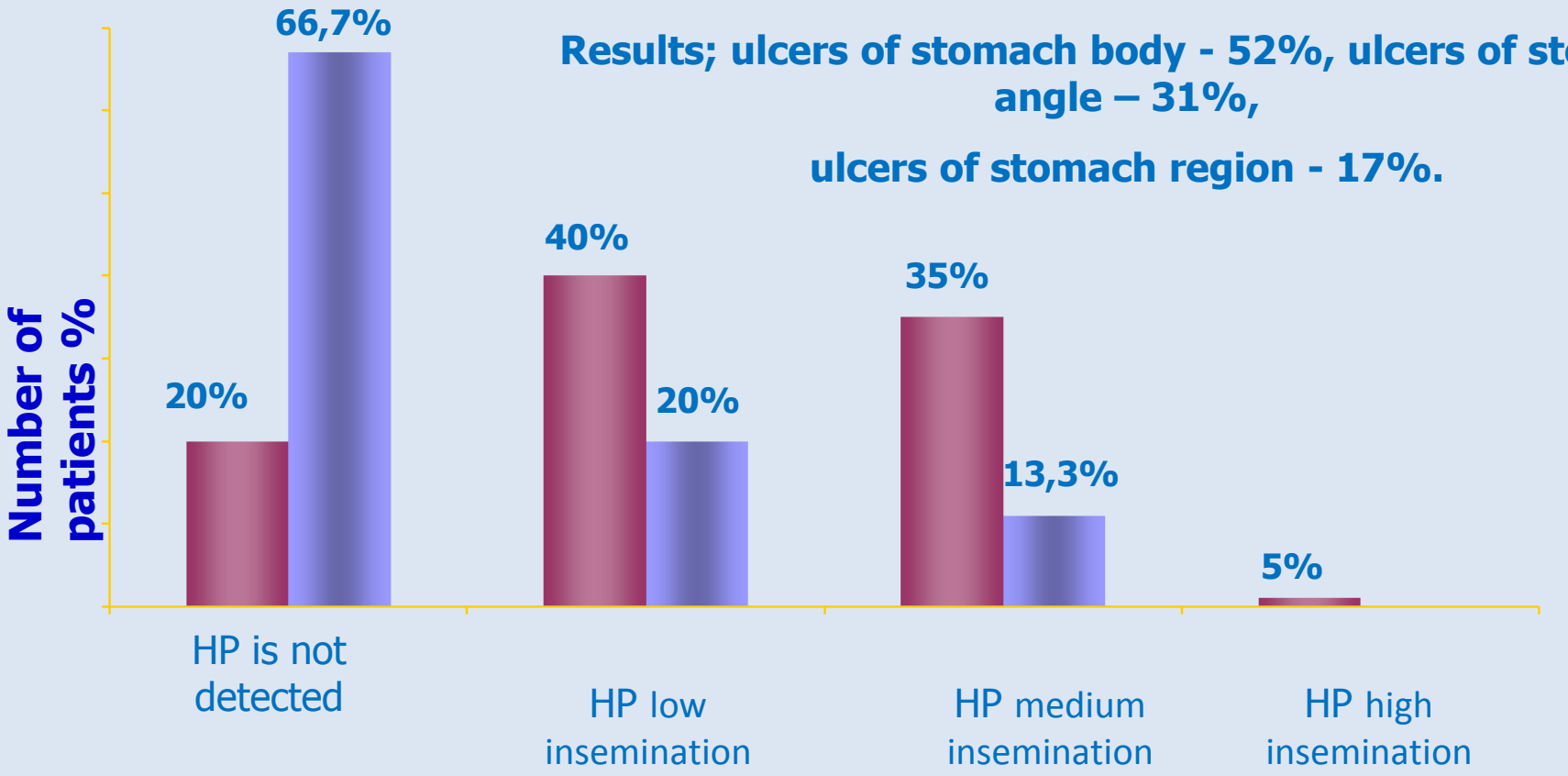
- **Histological mucosal samples were examined in microscopy 240, 360, 640 X**
- **The mucosal rate of HP (Helicobacter Pylori) was evaluated according to the following criteria:**

  low insemination – less than 20 microbial bodies in focus,
  medium – from 20 to 50,
  high – more than 50 microbial bodies

MORPHOFUNCTIONAL CHARACTERISTICS OF MUCOSAL LAMELLA UNDER DIFFERENT METHODS OF ULCER TREATMENT

Research Institute of Clinical and Experimental Lymphology Novosibirk 2002

RESULTS ON THE PRESENCE OF H. pylori (HP)



Results; ulcers of stomach body - 52%, ulcers of stomach angle – 31%,

ulcers of stomach region - 17%.

polymethylsiloxane polyhydrate detoxification

Control Group

APPLICATION OF **polymethylsiloxane polyhydrate** ENTEROSORBENT IN COMPLEX TREATMENT OF BOWEL DYSBACTERIOSIS

Paliy, IG, Tchernobroviy VN, Shevchenko YN, Shifris IM
Vinnytsa State University, Ukraine, Vinnitsa, 2000

51 patients between 15 and 77 years of age were examined and treated for intestinal dysbiosis of various degrees of severity

These patients were treated with **conventional methods (diet, vitamins, eubiotic preparations depending on the results of medical tests), along with oral administration of polymethylsiloxane polyhydrate 3 times daily, between meals and away from the administration of other drugs (1,5 - 2 hours before meals, 2 hours after meals at least).**

On Day 5- 7 of illness, 43 patients (i.e. 94.3%) out of 50 (i.e. 98%) showed a total disappearance of pain symptoms, while 7 patients (i.e. 13.7%) showed a significant reduction of these symptoms.

……. The reports of microbiological tests on patients suffering from intestinal dysbiosis and treated with polymethylsiloxane polyhydrate have shown that 100% of the patients showed normalization of intestinal microbiocenosis at the end of treatment.

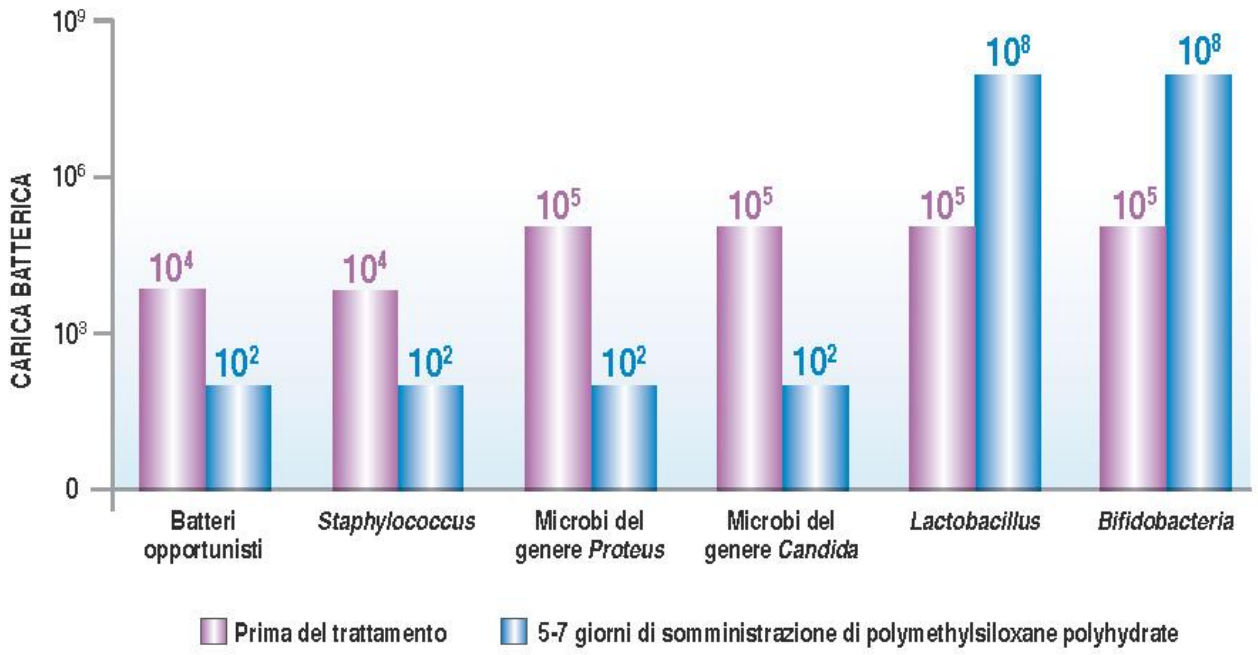
No patients treated with polymethylsiloxane polyhydrate showed complications. No side effects were reported: no vomiting, no allergic reactions, no exacerbation of pre-existing allergic reactions.

Tratto da: Chernobrovyj V.M., Palij I.G., Shevchenko Yu.N., Shifris I.M. – "polymethylsiloxane polyhydrate application in the integrated treatment of intestinal disbacteriosis - Russian Journal of Gastroenterology, Hepatology, Coloproctology, v. X, n°5 2000, 145.

APPLICATION OF polymethylsiloxane polyhydrate ENTEROSORBENT IN COMPLEX TREATMENT OF BOWEL DYSBACTERIOSIS

Paliy, IG, Tchernobroviy VN, Shevchenko YN, Shifris IM
Vinnytsa State University, Ukraine, Vinnitsa, 2000

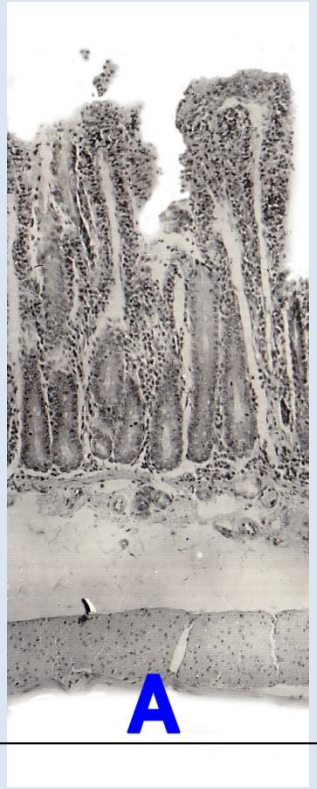
DYSBIOSIS TREATMENT



From: Chernobrovyj V.M., Palij I.G., Shevchenko Yu.N., Shifris I.M. – "**polymethylsiloxane polyhydrate** application in the integrated treatment of intestinal disbacteriosis - Russian Journal of Gastroenterology, Hepatology, Coloproctology, v. X, n°5 2000, 145.

Action of polymethylsiloxane polyhydrate on the mucosa of the small intestine

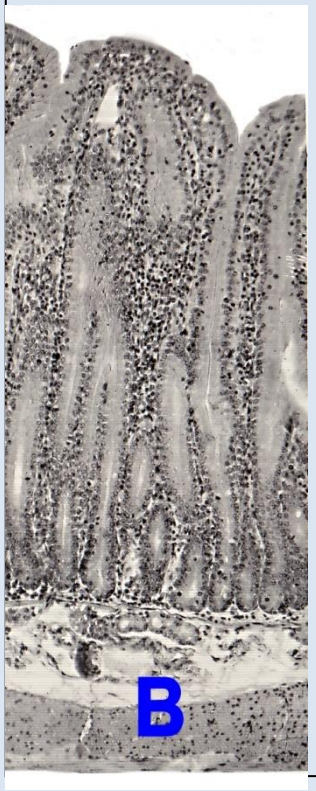
A. No polymethylsiloxane polyhydrate



The result of microcirculatory restriction is an edema with erosive mucosal damage.

Reduction of cell proliferation

B. Sì polymethylsiloxane polyhydrate

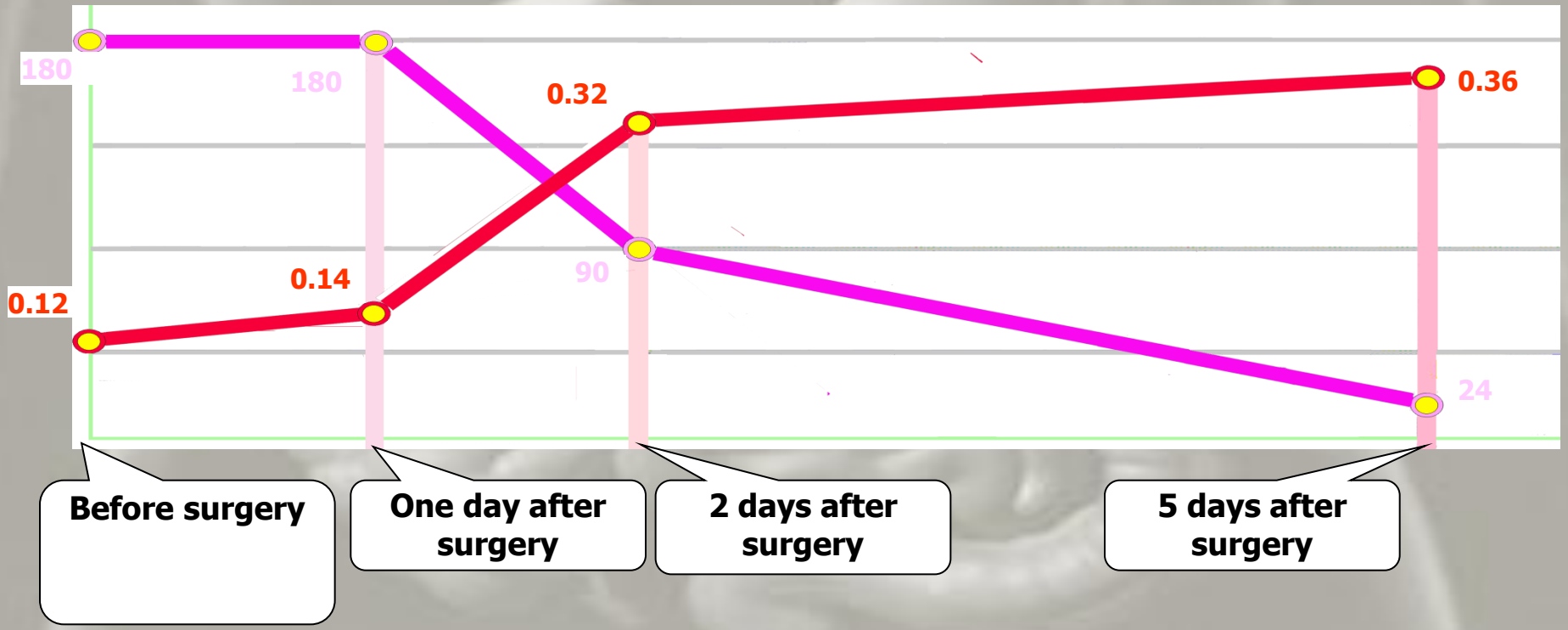


Improvement of microcirculation and repair of tissue damage

Pasechka N.V. The stabilizing effect of polymethylsiloxane polyhydrate on the structural bases of membrane digestion and absorption in the small intestine in severe thermal skin burns. Fiziol.Zh 1996 ;42(5-6):94-100. Ukrainian Pubmed –indexed for Medline

Use of Polymethylsiloxane polyhydrate in postsurgical period among patients with enteral insufficiency (during the lavage).

Increased secretory IgA *(sIgA)*
indicates the recovery of mucosal activity



Level of secretory IgA (sIgA)

Livello di antigeni nel piccolo intestino

New approaches:

Collection of articles and Clinical studies ALLERGOLOGY IMMUNOLOGY DERMATOLOGY 2015

POLYMETHYSILOXANE POLYHYDRATE

Introduction by:

Dr. Jaromir Bystron: "Allergologist: Allergy and Clinical Immunology Society (CSAKI) Czech Republic.

MINI-REVIEW

Detoxifying potential and clinical efficacy of the enterosorbent polymethylsiloxane polyhydrate in some diseases in children and adults

N.V. Nagornaya, A.V. Dubovaya

PUBLISHED ARTICLES:

Correction of systemic endotoxemia in childen with Atopic Dermatitis

B.A. Shamov, T.G. Malanicheva , O.F. Melnykov, L.V. Zabrodska, M.D. Tymchenko, T.V. Sydorenko, O.A. Naumova

Enterosorption in the treatment of children atopic Dermatitis complicated by fungal infection

G. Malanicheva, L.A. Khaertdinova

NEW STUDY REPORT 2015

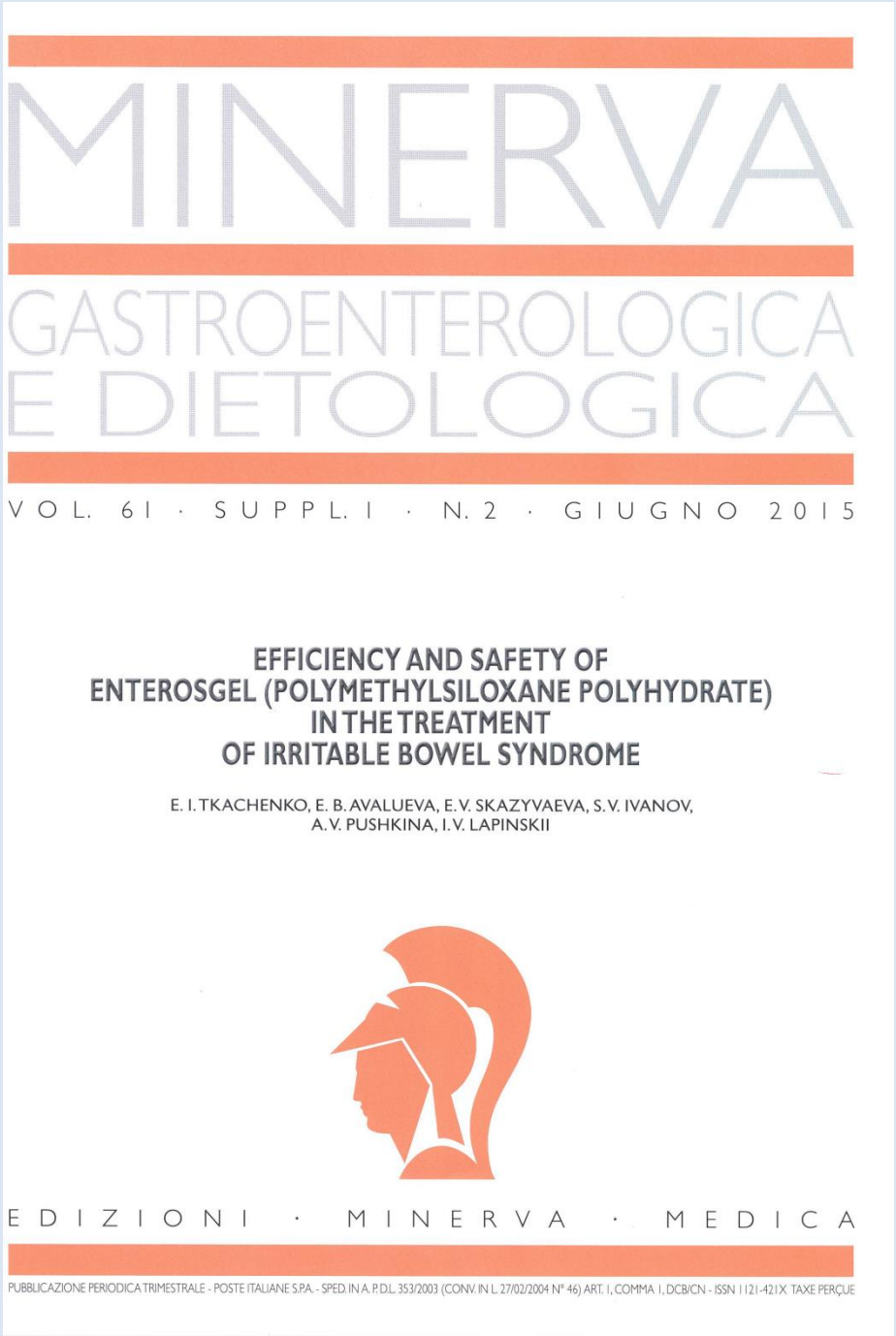
A.A. Baranov, N.A. Geppe, A.V. Karpushkina

Enterosorption with Polymethylsiloxane polyhydrate in the complementary treatment of allergies

J. Bystron

Prevention of asthma accompanied by high levels of heavy metals and aldehydes in children affected by recurrent bronchitis with recurrent wheezing.

N.V. Zaytseva, A.I. Aminova, O. Yu. Ustinova, A.A. Akatova, K.P. Luzhetskiy



New publication:

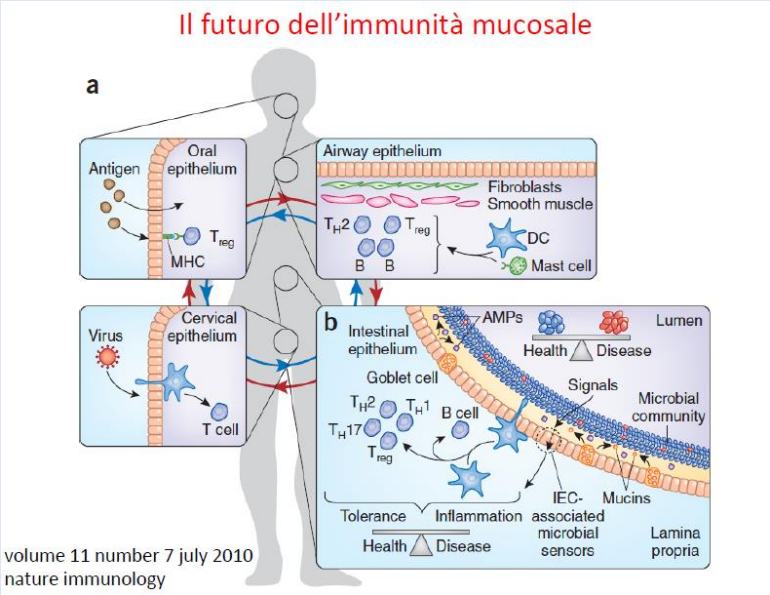
Observational study in 30 patients with IBS

It significantly reduces the episodes of diarrhea, abdominal pain, dyspepsia, by normalizing the bowel function.

Physiological Nutraceuticals

"3Rs" Treatment
CENTRAL ROLE OF THE INTESTINE

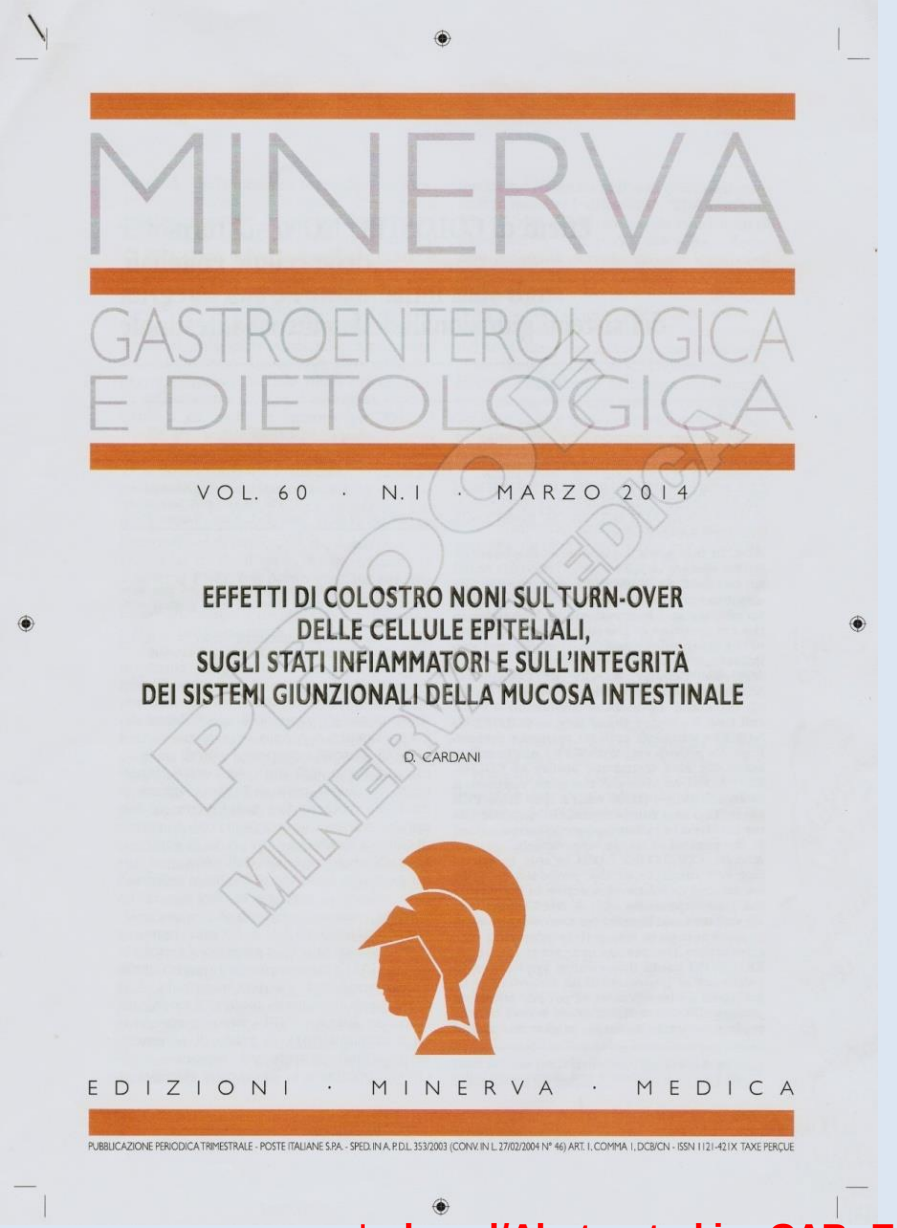
REMOVE TOXINS FROM THE DIGESTIVE TRACT



REPLACE THE MICROBIOTA

REPAIR

THE GASTRO-INTESTINAL MUCOSA



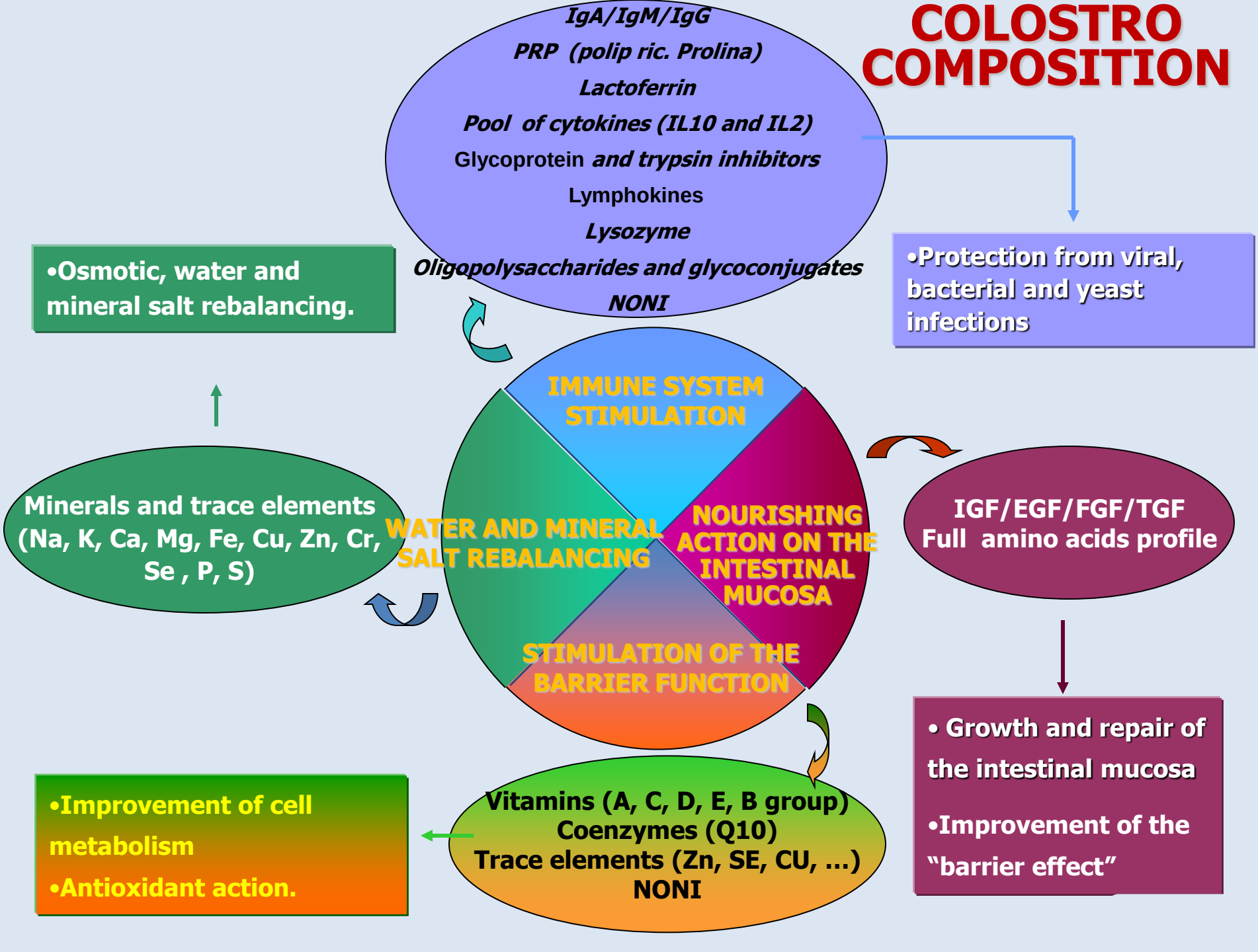
"3R" treatment intestinal homeostasis REPAIR

Department of Biomedical Sciences for Health " Città Studi" University of Milan, Italy

Presented at
"Pianeta Nutrizione" 2015
International Congresses

Indexed/Abstracted in: CAB, EMBASE, PubMed/MEDLINE, Scopus

COLOSTRO COMPOSITION



Wang MY et Al. "Morinda citrifolia (Noni)" : a literature review and recent advances in Noni reserach"
University of Illinois College of Medicine
Acta Pharmacol Sin 2002 Dec;23(12):1127-1141

- Tropical plant traditionally used in Polynesia for over 2000 years
- All parts of the plant were used, while fruits were eaten for their beneficial properties
- **Morinda citrifolia fruit juice powder: contains many components identified as terpenoids, alkaloids, potassium, Vitamin C and A, glycosyl flavones, rutin, proxeronine**

antibacterial, antiviral, antifungal, antitumor, antihelmin, analgesic, hypotensive, anti-inflammatory, and immune enhancing effects.

- alkaloid
- ***PROXERONINE***

Proxeroninase

CHANGES DIFFERENT PROTEIN STRUCTURES

- **XERONINE**

HELPS PROPER FUNCTIONING OF DIFFERENT MOLECULES

MATERIALS AND METHODS: 2 cells cluster:

✓EVALUATION OF COLON CELL TURNOVER

In vitro model of intestinal ephitelium *cell CACO_2 from human colorectal carcinoma in broth culture*

4 cell groups:

Group 1 : STARVED : cell cultivated in a basal medium with no complement

Group 2: UNTR: cells cultivated in a complete medium

Group 3: COLOSTRO: cells cultivated in a complete medium with the addition of 2% Colostrum 2%

Group 4: COLOSTRO NONI: cells cultivated in a complete medium with the addition of 2% COLOSTRO NONI .
Carried out in quadruple form

MATERIALS AND METHODS

•EVALUATION OF THE PHYSIOLOGICAL EXPRESSION OF IL-8

In vitro model of intestinal epithelium cell CACO_2 from human colorectal carcinoma up to one-layer epithelial enterocytes development

4 cell groups:

Group 1: UNTR cell cultivated in a basal medium with no complement
Group 2: TNF-cells cultivated in a complete medium with TNF-a 100 ng / ml;
Group 3: TNF-a 100 ng / ml + 2% COLOSTRUM;
Group 4: TNF-a 100 ng / ml + 2% COLOSTRO NONI.

"Effects of a combination of bovine colostrum and Morinda Citrifolia extract (Noni) on proliferation of human coloncytes "

normale mostrano un lieve incremento della crescita (UNTR: 115±3%). Il trattamento con solo colostro mostra un aumento delle capacità proliferative significativo (COLOSTRO:

L'aggiunta al terreno di coltura del solo Colostro (2%) in presenza di TNF-α (TNF-α+COL) non modifica in modo statisticamente significativo il livello di mRNA di IL-8 (Figura 2).

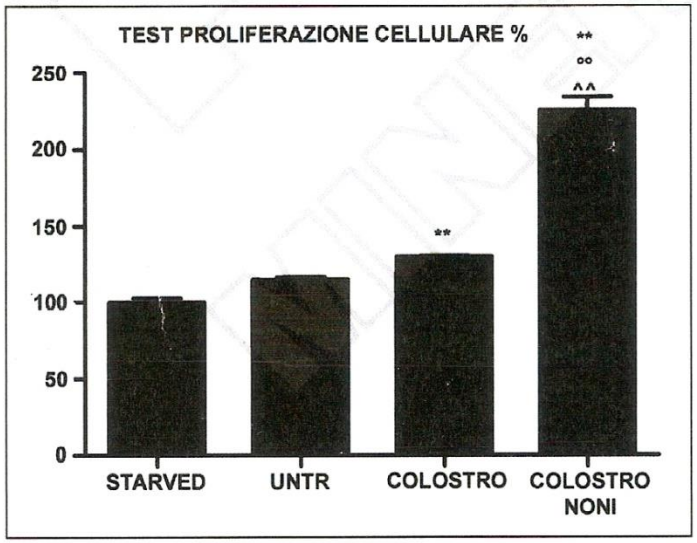
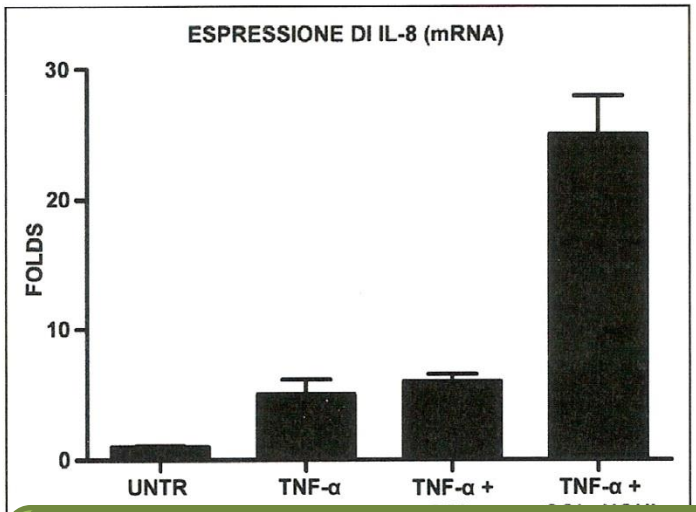


Figura 1. — Analisi della curva di crescita cellulare nelle diverse condizioni di trattamento. Emerge chiaramente la capacità di stimolazione del turn-over cellulare di COLOSTRO NONI su cellule Caco-2 in coltura, meccanismo fondamentale nella riparazione dei danni epiteliali.



The increase of IL-8 by the enterocytes maintains expression levels (+25 levels of increase) far below those normally recorded in the presence of infections (+ 300/600 levels).

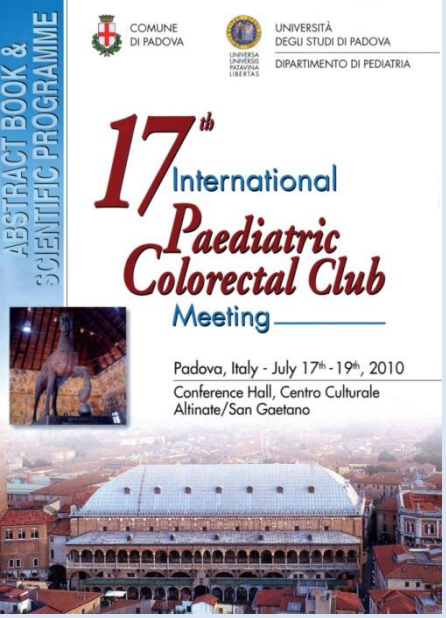
IL-8, also known as *neutrophil chemotactic factor*, has two primary functions: it induces chemotaxis in target cells, primarily neutrophils but also other granulocytes, causing them to migrate toward the site of infection. IL-8 also induces phagocytosis once they have arrived. And it is involved in **angiogenesis** phenomena and **migration of epithelial cells and restoration of normal cell turnover**.

Conclusions: REPAIR

The results shown in Figure 1 **illustrate how Colostro Noni is able to balance the turn-over of epithelial cells in an in vitro experimental model.**

The regulation of cell proliferation is essential to support the function of **protection and re-epithelialisation of the gastrointestinal tract due to the epithelium damage and is mediated by lactoferrin**, a protein present in colostrum and involved in a great number of cellular processes including the immune response to bacterial and viral infection, and also the stimulation of the proliferation and cellular differentiation.

No side effects secondary to the use of freeze-dried bovine colostrum and Morinda citrifolia juice are reported in Literature, indeed preliminary data on post-surgical prophylaxis in subjects affected by Hirschsprung's disease show the product safety also in growing subjects, such as children



Enterocolitis secondary to HIRSCHSPRUNG'S DISEASE COMPLICATIONS (HD): preliminary results in the post-surgical prophylaxis with Colostro Noni

F. Grandi*, P. Betalli*, P. Midrio*, F. Fascetti-Leon**, PG. Gamba*
*Paediatric Surgery; University Hospital of Padua, Padua, Italy
**Paediatric Surgery Unit, IRCCS Hospital San Matteo, Pavia, Italy

5 pts with HD : Average age at surgery: 3.27 months
Average days of hospitalization: 7.25 days

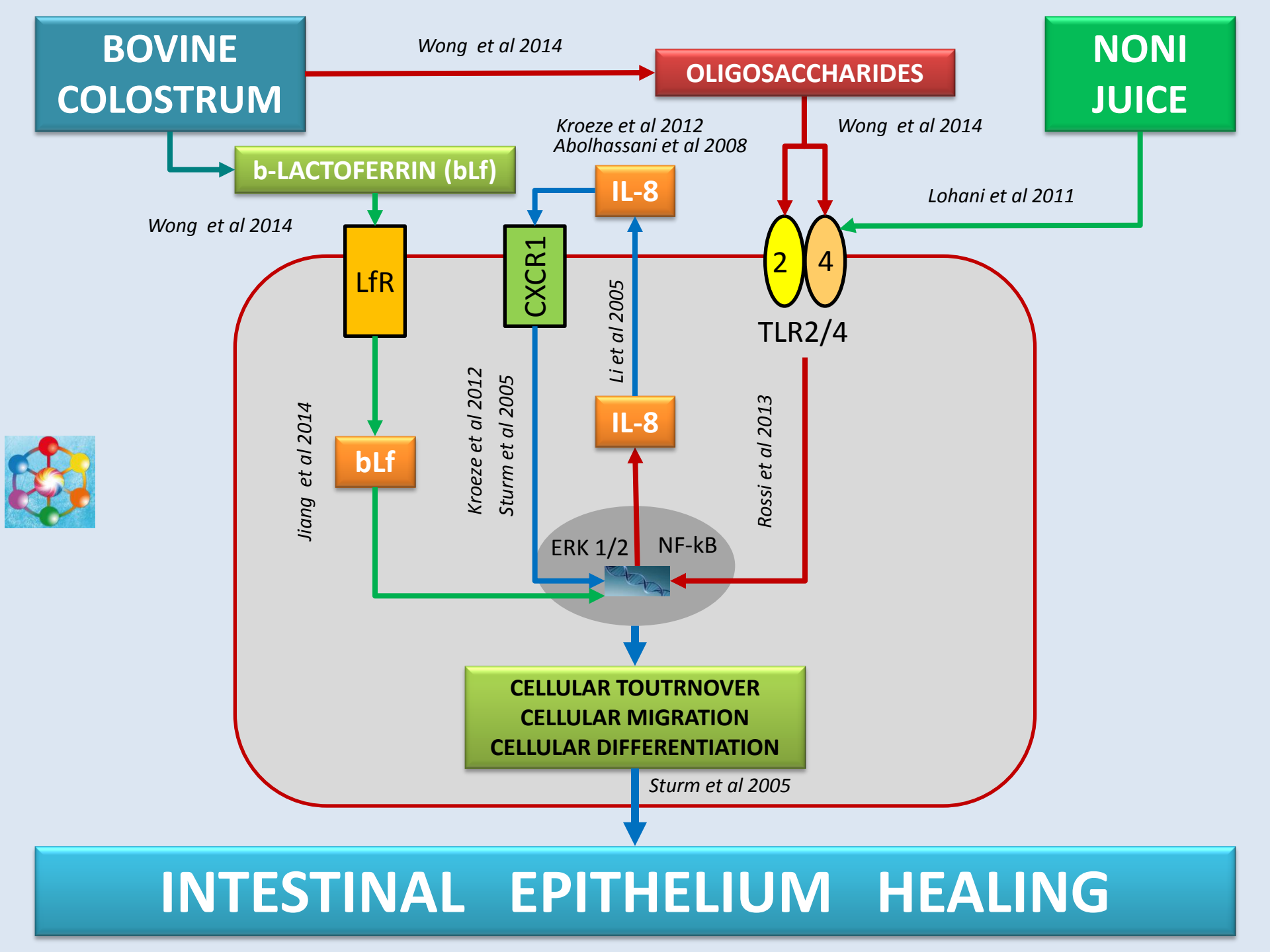
✓Incidence of post-surgical complications: gastroenteritis 34%

- ✓ 1 month after surgery all patients take COLOSTRO NONI ®
- ✓ 2 times / day for 15 days, then 1 time / day for 45 days

***RESULTS* : Clinical evaluation at 1,3,6 months after surgery**

Statitistical data and severity of enterocolitis episodes were evaluated according to literature parameters *

No episodes of enterocolisits were reported in the follow –up of 12 months


BOVINE COLOSTRUM
Wong et al 2014
OLIGOSACCHARIDES
NONI JUICE
Kroeze et al 2012
Abolhassani et al 2008
Wong et al 2014
b-LACTOFERRIN (bLf)
IL-8
Lohani et al 2011
Wong et al 2014
LfR
CXCR1
2
4
TLR2/4
Li et al 2005
Jiang et al 2014
Kroeze et al 2012
Sturm et al 2005
IL-8
Rossi et al 2013
bLf
ERK 1/2
NF-kB
CELLULAR TOUTRNOVER
CELLULAR MIGRATION
CELLULAR DIFFERENTIATION
Sturm et al 2005
INTESTINAL EPITHELIUM HEALING

Physiological Nutraceuticals

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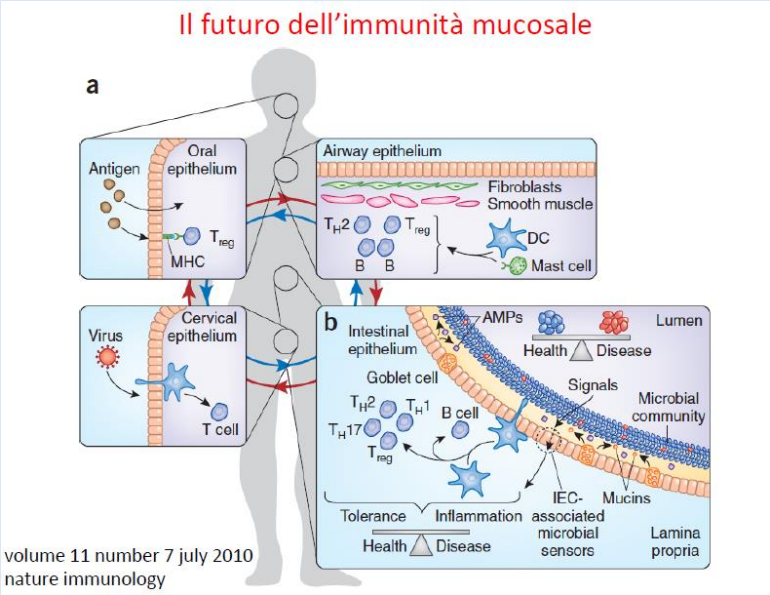
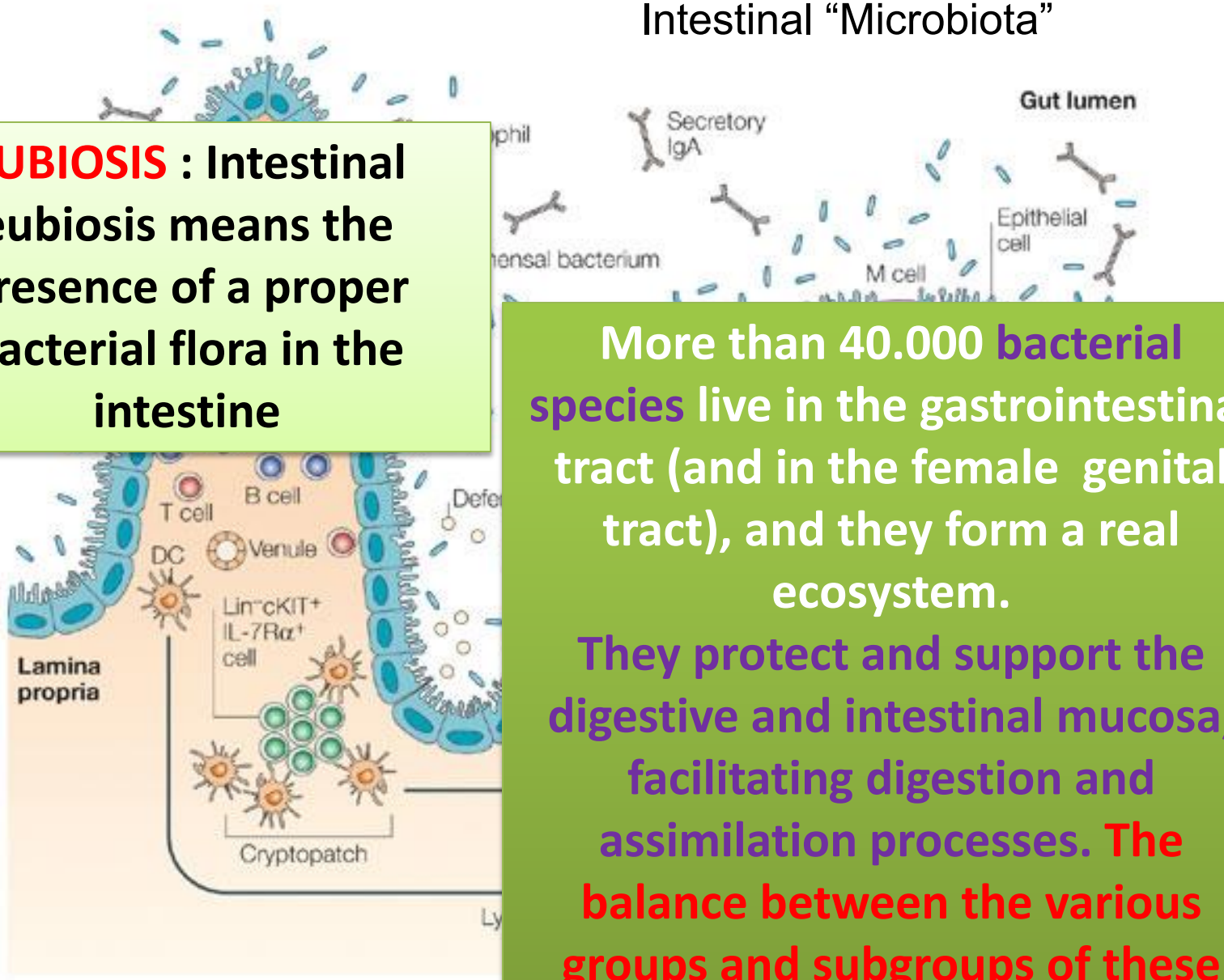


REPLACE THE MICROBIOTA

REPAIR
THE GASTRO-INTESTINAL MUCOSA

Intestinal “Microbiota”

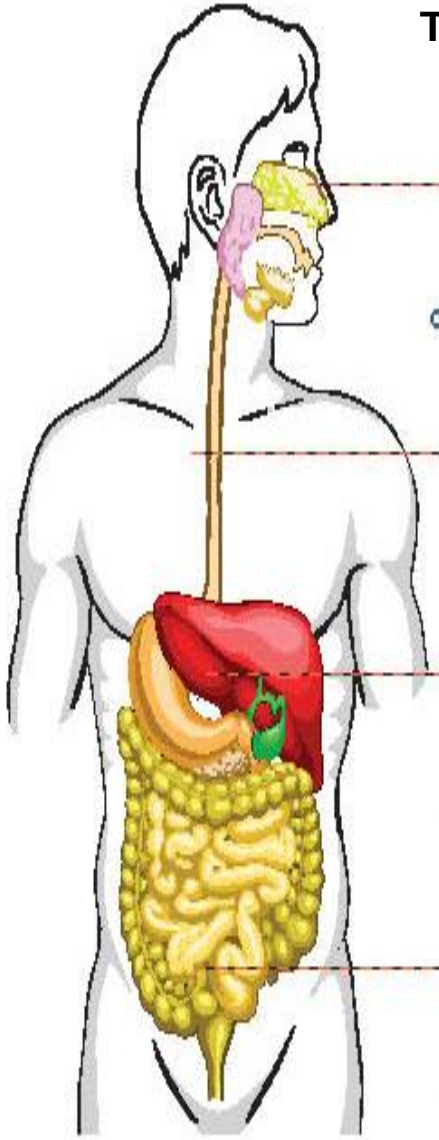
EUBIOSIS : Intestinal eubiosis means the presence of a proper bacterial flora in the intestine



More than 40.000 bacterial species live in the gastrointestinal tract (and in the female genital tract), and they form a real ecosystem.

They protect and support the digestive and intestinal mucosa, facilitating digestion and assimilation processes. The balance between the various groups and subgroups of these BACTERIA is essential to your health.

The Human Microbiota Composition

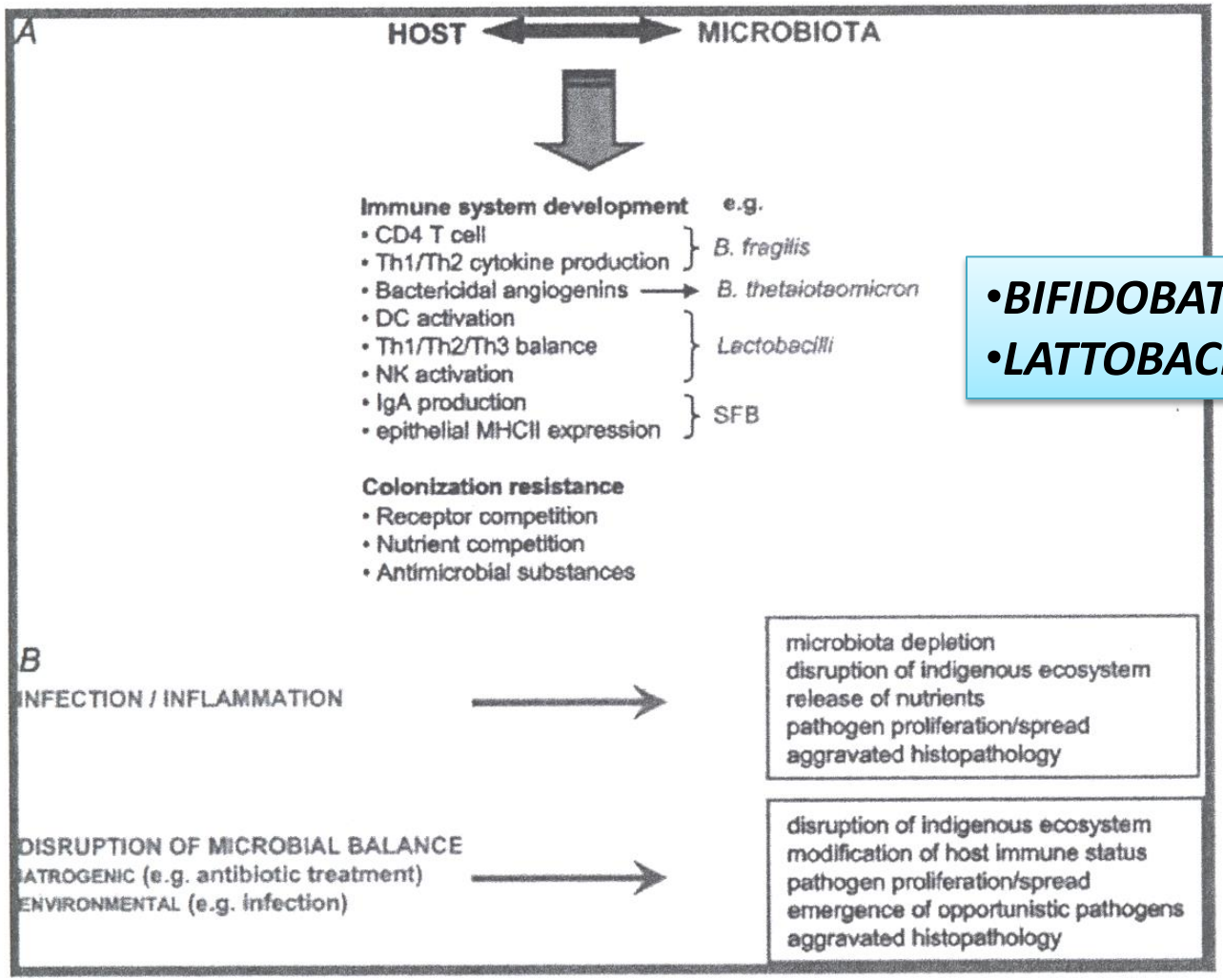


	tempo di transito	pH	quantità microrganismi/ml	gruppi microbici	processi microbici	processi fisiologici
cavo orale (saliva)			10^6-10^8	streptococchi, batteroidi, bacilli lattici, peptostreptococchi, clostridi, lieviti		digestione
stomaco	15 - 20 minuti	2 - 3	10^2-10^3	bacilli lattici, streptobatteri, helicobacter pylori lieviti		digestione
piccolo intestino	2 - 3 ore	4 - 8	duodeno 10^2-10^3 digiuno 10^3-10^5 ileo 10^4-10^8	bacilli lattici, streptobatteri, bifidobatteri, enterococchi, batteroidi, clostridi	proteolisi e saccarolisi limitata produzione di tossine e SCFA*	assorbimento minerali, zuccheri, aminoacidi altri principi nutritivi
colon	24 - 72 ore	7 - 9	10^{13}-10^{14}	bacilli lattici, streptococchi, enterobatteri bifidobatteri, batteroidi, clostridi, lieviti, peptococchi, ruminococchi, fusobatteri, lubatteri, Atopobium	intensa proteolisi e saccarolisi, tossine e SCFA*	assorbimento acqua, minerali, acidi organici

Interazioni batteriche e fisiochimiche in aree differenti del tratto gastro-intestinale di adulto (fonte: modificato da Gibson e Rastell)

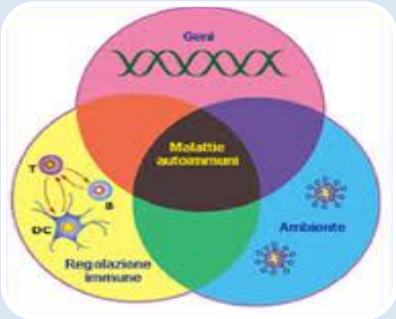
* *Acidi Grassi a Catena Corta*

The role of the intestinal microbiota in host immune development and infection progression



- ***BIFIDOBATTERI***
- ***LATTOBACILLI***

Inna Sekirov et al: J Physiol 587.17 (2009) pp 4159–4167



DYSBIOSIS : Progressive disorganization of the intestinal microflora *

DYSBIOSIS MAY RESULT IN:

- ✓IMBALANCE OF MICROBIAL COMPOSITION AND PREVALENT PATHOGENS
- ✓DIGESTIVE AND ABSORPTION DISORDERS
- ✓**INFECTIONS :** INTESTINAL, GENITAL AND GENERAL
- ✓ IMMUNE RESPONSE ALTERATIONS

***Gebbers 1981**

Eligibility criteria for the selection of a probiotic :

- **have human origin**
- **show a non-pathogenic effect (even in immunocompromised patients)**
- **withstand the technological processes of preparation, the acid gastric environment and the bile**
- **colonize and proliferate within the gastrointestinal tract or other mucous cavities selected as a habitat**
- **produce antimicrobial substances, modulate immune responses and influence metabolic activities**
- **prove to have nutritional and therapeutic effects***

PROBIOTICS MUST HAVE PRECISE CHARACTERISTICS IN ORDER TO ACT BENEFICIALLY ON HEALTH
Expert Consultation FAO/WHO Guidelines,
Ministry of Health

***FAO/WHO / Ministery of Health : USEFUL DOSAGE amount 10^9 CFU/ml**

Evaluation of the Intestinal Colonization by Microencapsulated Probiotic Bacteria in Comparison With the Same Uncoated Strains

Mario Del Piano, MD, Stefania Carmagnola, MD,* Silvano Andorno, MD,* Michela Pagliarulo, MD,* Roberto Tari, MD,* Luca Mogna, BS,† Gian Paolo Strozzi, BS,‡ Filomena Sforza, MD,§ and Lucio Capurso, MD‖*

Objective: to estimate the quantitative kinetics of colonization of 2 probiotic strains , *L. plantarum* LP01 (LMG P -21021) and *B. breve* BR03 (DSM 16604) **administered in non-microencapsulated and microencapsulated forms**

- Cross-over, double-blind, randomized study
  44 healthy volunteers divided into 2 groups (A21 + B 21)
- Group A : took a mix of **L. Plantarum LP01** +B.breve BR03 ; **non-microencapsulated 5x10 UFC**
- Group B : took a mix of **L. Plantarum LP01** +B.breve BR03 ; 1**x10 CFU gastroprotected microencapsulated**

Duration : 21 days + 3 weeks washout + exchange

- **Evaluation based on fecal bacterial counts**

J Clin Gastroenterol • Volume 44, Supp. 1, September 2010

J Clin Gastroenterol . 2012 Ottobre ; 46 Suppl : S85 - 92 . doi : 10.1097/MCG.0b013e3182672796 .

Evaluation of the intestinal colonization by microencapsulated probiotic bacteria in comparison with the same uncoated strains.

Del Piano M[1], Carmagnola S, Andorno S, Pagliarulo M, Tari R, Mogna L, Strozzi GP, Sforza F, Capurso L.
[1]Department of Gastroenterology, Gastroenterology Unit, Maggiore della Carità Hospital, Novara, Italy.

- Double-blind, randomized, crossover study
- 53 healthy volunteers divided into 2 groups (A21 + B 21)
- Group A (27 subjects) mix of probiotic strains: Lactobacillus acidophilus LA02 (DSM 21717), Lactobacillus rhamnosus LR04 (DSM 16605) , L.actobacillus rhamnosus GG, or LGG (ATCC 53103) , Lactobacillus rhamnosus LR06 (DSM 21981) , and Bifidobacterium lactis BS01 (MG P - 21384), **in non-microencapsulated** form, total amount **5x10 9 CFU**
- Group B (26 subjects) mix of probiotic strains: Lactobacillus acidophilus LA02 (DSM 21717), Lactobacillus rhamnosus LR04 (DSM 16605) , L.actobacillus rhamnosus GG , o LGG (ATCC 53103) , Lactobacillus rhamnosus LR06 (DSM 21981) , and Bifidobacterium lactis BS01 (MG P - 21384), in **microencapsulated** form, total amount 1**x10 9 CFU gastro-protected microencapsulated**

  Duration: 21 days 3 weeks washout + exchange
- **Evaluation based on fecal bacterial counts**

Evaluation of the Intestinal Colonization by Microencapsulated Probiotic Bacteria in Comparison With the Same Uncoated Strains

Mario Del Piano, MD,* Stefania Carmagnola, MD,* Silvano Andorno, MD,* Michela Pagliarulo, MD,* Roberto Tari, MD,* Luca Mogna, BS,† Gian Paolo Strozzi, BS,‡ Filomena Sforza, MD,§ and Lucio Capurso, MD||

J Clin Gastroenterol . 2012 Ottobre ; 46 Suppl : S85 - 92 . doi : 10.1097/MCG.0b013e3182672796

Evaluation of the intestinal colonization by microencapsulated probiotic bacteria in comparison with the same uncoated strains.

RESULTS:

- measured and demonstrated probiotic gut colonization of strains
- improved kinetics of colonization of microencapsulated gastroprotected strains vs. those non-gastroprotected

MICROENCAPSULATED PROBIOTICS

100% live in the gut !!!!

TABLE 1. Quantification of Fecal Lactobacilli and Bifidobacteria (m ± SEM, Log_{10} CFU/g) Before and After the 2 Treatment Periods, Including the Washout Phase

Time	Group A Log CFU/g	Group A P†	Group B Log CFU/g	Group B P†
a) Comparison between time zero (d_0), or d_{42}, and the following analysis within each group				
d_0				
Lactobacilli	5.53 ± 0.23	*	5.47 ± 0.20	*
Bifidobacteria	7.94 ± 0.23	*	8.25 ± 0.19	*
d_{10}				
Lactobacilli	6.89 ± 0.12	< 0.0001	6.87 ± 0.19	< 0.0001
Bifidobacteria	9.26 ± 0.13	0.0001	9.21 ± 0.17	0.0008
d_{21}				
Lactobacilli	7.32 ± 0.13	< 0.0001	7.10 ± 0.14	< 0.0001
Bifidobacteria	9.47 ± 0.10	< 0.0001	9.43 ± 0.12	< 0.0001
d_{42}				
Lactobacilli	5.61 ± 0.23	*	5.75 ± 0.21	*
Bifidobacteria	8.05 ± 0.23	*	8.44 ± 0.17	*
d_{52}				
Lactobacilli	7.13 ± 0.14	< 0.0001	6.96 ± 0.15	< 0.0001
Bifidobacteria	9.38 ± 0.09	0.0001	9.19 ± 0.16	0.003
d_{63}				
Lactobacilli	7.41 ± 0.13	< 0.0001	7.20 ± 0.13	< 0.0001
Bifidobacteria	9.63 ± 0.08	< 0.0001	9.47 ± 0.08	< 0.0001
b) Comparison between the 2 groups at d_0 and following analysis				P‡ (A vs. B)
d_0				
Lactobacilli	5.53 ± 0.23		5.47 ± 0.20	0.85
Bifidobacteria	7.94 ± 0.23		8.25 ± 0.19	0.29
d_{10}				
Lactobacilli	6.89 ± 0.12		6.87 ± 0.19	0.92
Bifidobacteria	9.26 ± 0.13		9.21 ± 0.17	0.83
d_{21}				
Lactobacilli	7.32 ± 0.13		7.10 ± 0.14	0.26
Bifidobacteria	9.47 ± 0.10		9.43 ± 0.12	0.81
d_{42}				
Lactobacilli	5.61 ± 0.23		5.75 ± 0.21	0.53
Bifidobacteria	8.05 ± 0.23		8.44 ± 0.17	0.34
d_{52}				
Lactobacilli	7.13 ± 0.14		6.96 ± 0.15	0.41
Bifidobacteria	9.38 ± 0.09		9.19 ± 0.16	0.30
d_{62}				
Lactobacilli	7.41 ± 0.13		7.20 ± 0.13	0.27
Bifidobacteria	9.63 ± 0.08		9.47 ± 0.08	0.18

CFU indicates colony forming units.
*Comparison reference time (d_0 for the first treatment period and d_{42} for the second one).
†Comparison between time zero (d_0), or d_{42}, and the following analysis within each group.
‡Comparison between the 2 groups at d_0 and following analysis.

- MAXIMUM STABILITY AND VIABILITY OF THE STRAINS:
- HIGH DOSES ARE NOT NEEDED

- 6 probiotics specifics and unique probiotics strains sinergy
- Everyone “gastroresistent microincapsulated”
  - with Prebiotic FOS
  - ALLERGEN FREE
  - L.salivarius LS03 help

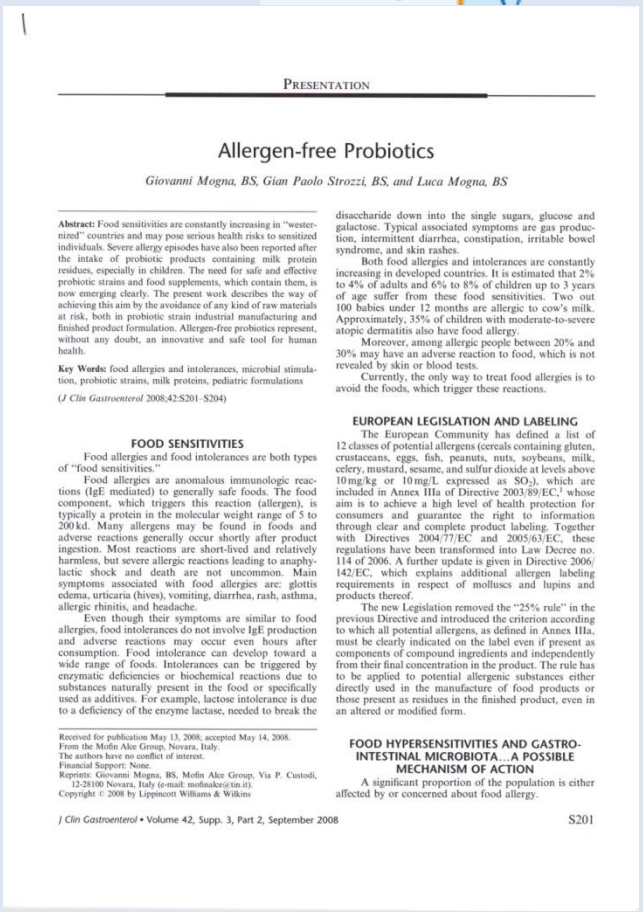
PRIVO DI ALLERGENI BREVETTATO PROBIOTICAL

INFORMAZIONI NUTRIZIONALI PER BUSTINA

Valore energetico	6,75 kcal (28,26 kJ)
Proteine	2,0 mg
Carboidrati	2336,5 mg
Grassi	17,6 mg
Frutto-oligosaccaridi a catena corta (FOSsc)	1500 mg

Bifidobacterium lactis BS01, *Lactobacillus acidophilus* LA02, *Lactobacillus paracasei* LPC00, *Lactobacillus plantarum* LP02, *Lactobacillus rhamnosus* LR06, *Lactobacillus salivarius* LS03

carica per bustina: ≥2 MLD



PRESENTATION

Allergen-free Probiotics

Giovanni Mogna, BS, Gian Paolo Strozzi, BS, and Luca Mogna, BS

Abstract: Food sensitivities are constantly increasing in “westernized” countries and may pose serious health risks to sensitized individuals. Severe allergy episodes have also been reported after the intake of probiotic products containing milk protein residues, especially in children. The need for safe and effective probiotic strains and food supplements, which contain them, is now emerging clearly. The present work describes the way of achieving this aim by the avoidance of any kind of raw materials at risk, both in probiotic strain industrial manufacturing and finished product formulation. Allergen-free probiotics represent, without any doubt, an innovative and safe tool for human health.

Key Words: food allergies and intolerances, microbial stimulation, probiotic strains, milk proteins, pediatric formulations

(*J Clin Gastroenterol* 2008;42:S201–S204)

FOOD SENSITIVITIES

Food allergies and food intolerances are both types of “food sensitivities.”

Food allergies are anomalous immunologic reactions (IgE mediated) to generally safe foods. The food component, which triggers this reaction (allergen), is typically a protein in the molecular weight range of 5 to 200 kd. Many allergens may be found in foods and adverse reactions generally occur shortly after product ingestion. Most reactions are short-lived and relatively harmless, but severe allergic reactions leading to anaphylactic shock and death are not uncommon. Main symptoms associated with food allergies are: glottis edema, urticaria (hives), vomiting, diarrhea, rash, asthma, allergic rhinitis, and headache.

Even though their symptoms are similar to food allergies, food intolerances do not involve IgE production and adverse reactions may occur even hours after consumption. Food intolerance can develop toward a wide range of foods. Intolerances can be triggered by enzymatic deficiencies or biochemical reactions due to substances naturally present in the food or specifically used as additives. For example, lactose intolerance is due to a deficiency of the enzyme lactase, needed to break the disaccharide down into the single sugars, glucose and galactose. Typical associated symptoms are gas production, intermittent diarrhea, constipation, irritable bowel syndrome, and skin rashes.

Both food allergies and intolerances are constantly increasing in developed countries. It is estimated that 2% to 4% of adults and 6% to 8% of children up to 3 years of age suffer from these food sensitivities. Two out 100 babies under 12 months are allergic to cow’s milk. Approximately, 35% of children with moderate-to-severe atopic dermatitis also have food allergy.

Moreover, among allergic people between 20% and 30% may have an adverse reaction to food, which is not revealed by skin or blood tests.

Currently, the only way to treat food allergies is to avoid the foods, which trigger these reactions.

EUROPEAN LEGISLATION AND LABELING

The European Community has defined a list of 12 classes of potential allergens (cereals containing gluten, crustaceans, eggs, fish, peanuts, nuts, soybeans, milk, celery, mustard, sesame, and sulfur dioxide at levels above 10 mg/kg or 10 mg/L expressed as SO_2), which are included in Annex IIIa of Directive 2003/89/EC,[1] whose aim is to achieve a high level of health protection for consumers and guarantee the right to information through clear and complete product labeling. Together with Directives 2004/77/EC and 2005/63/EC, these regulations have been transformed into Law Decree no. 114 of 2006. A further update is given in Directive 2006/142/EC, which explains additional allergen labeling requirements in respect of molluscs and lupins and products thereof.

The new Legislation removed the “25% rule” in the previous Directive and introduced the criterion according to which all potential allergens, as defined in Annex IIIa, must be clearly indicated on the label even if present as components of compound ingredients and independently from their final concentration in the product. The rule has to be applied to potential allergenic substances either directly used in the manufacture of food products or those present as residues in the finished product, even in an altered or modified form.

FOOD HYPERSENSITIVITIES AND GASTROINTESTINAL MICROBIOTA…A POSSIBLE MECHANISM OF ACTION

A significant proportion of the population is either affected by or concerned about food allergy.

Received for publication May 13, 2008; accepted May 14, 2008.
From the Mofin Alce Group, Novara, Italy.
The authors have no conflict of interest.
Financial Support: None.
Reprints: Giovanni Mogna, BS, Mofin Alce Group, Via P. Custodi, 12-28100 Novara, Italy (e-mail: mofinalce@tin.it).

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

17 Maggio 2016

A supplementation of Lactobacilli and Bifidobacteria (formulation 6 strains) associated with fructo-oligosaccharides(FOS) reduces ocular surface damage

40 patients were enrolled with **Dry Eye Disease *(DED)*** — constant irritation, foreign body sensation, blurred vision and poor ability to work and perform daily activities

Group A
20 patients

Group B
20 patients

Treated with artificial tears

Treated with artificial tears + **(formulation 6 strains + FOS)** (*Bifidobacteria and Lactobacilli)*

RESULTS

After treatment, the patients enrolled in the study showed a reduction of Staphylococcus aureus aas well as a reduction of aerobic Gram-negative bacteria associated with a reduction of DED.

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Fields of application of **polymethylsiloxane polyhydrate and "3R" TREATMENT in adults and children as detoxifying method, effective and safe treatment to recover the intestinal and organ: *REMOVE-REPAIR-REPLACE***

- Gastrointestinal and toxicological area: peptic and duodenal ulcer, inflammatory bowel syndrome, malabsorption syndrome, dysbacteriosis (normalization of microbiocenosis with normalization of the bowel function, eradication of pathogenic microflora) food, alcohol, aromatic hydrocarbon, salts of heavy metals and radionuclide poisoning. Antioxidant action.
-
- Infectious area: bacterial and viral enteritis, enterocolitis and gastroenteritis (salmonellosis, dysentery, rotavirus), viral hepatitis
- Dermo-allergy area: sensitization and food allergy, atopic eczema, allergic asthma, atopic dermatitis.
- Gynecological area: candidiasis, acute and chronic urogenital infections

55 PUBLICATIONS AND STUDIES INDEXED IN PUBMED

WORK –IN PROGRESS ...

TAKE HOME MESSAGE :

Modulazione dell'omeostasi intestinale

- Intestinal homeostasis = health hub
- Physiological Nutraceuticals new nutraceutic treatment :
- "3R" treatment : Remove-Repare-Replace
- Remove : toxins, allergens, pathogenic bacteria
- Repare : intestinal mucosa
- Replace : Microflora health

Recovery of perfect homeostasis with

Physiological Nutraceuticals

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