E. Biffi

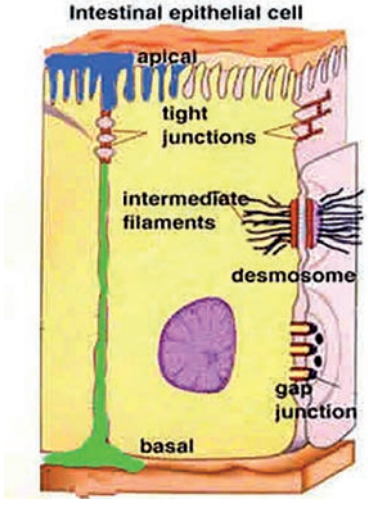
FROM DYSBIOSIS TO LOW GRADE CHRONIC INFLAMMATION

– EFFECTS OF COLOSTRO NONI ON THE TURNOVER OF EPITHELIAL CELLS ON INFLAMMATORY CONDITIONS AND THE INTEGRITY OF INTESTINAL MUCOSA JUNCTIONAL SYSTEMS

SUMMARY

It is here considered the importance of the intestinal barrier in the context of Innate Immunity and in the regulation of the Microbiota Brain Gut Axis (MGBA), then it is examined the role played by increased intestinal permeability in the pathogenesis of important and widespread intestinal and systemic diseases whose different clinical expressions is essentially linked to the interaction between genetic and epigenetic factors.
Among the causes of increased intestinal permeability, some are particularly widespread and frequent, such as stress and the use of NSAID, with or without pump inhibitors.
All these are associated with increased intestinal permeability, which makes it an extremely widespread phenomenon, especially in Western populations.
Hence, the need to identify treatments that can prevent or treat the damage of the intestinal barrier.
Numerous studies, including the last one conducted at the Biomedical Science Department of the University of Milan (Italy) have shown the capacity of the association of colostrum with Noni (*Morinda citrifolia*) to stimulate the repair of the intestinal barrier and the immune-modulating ability.

KEY WORDS **DYSBIOSIS, LOW GRADE CHRONIC INFLAMMATION, JUNCTIONAL SYSTEMS, INTESTINAL MUCOSA, COLOSTRO NONI**



http://www.bio.davidson.edu/bernd/Lab/EpithelialInfoWeb/epithelia%20structure.jpg

The close relationship between the intestinal microbiota and the human body that houses it has had an impact on the phylogenetic and ontogenetic creation of differentiated relational structures able to permit the establishment of complex functional fields involved in the regulation of the whole Psycho-Neuro-Endocrine-Immune (PNEI) System.

– In the relationship between neuroendocrine structures and intestine this allows to envisage a real regulation network whose functions are extremely delicate and complex: the **Microbiota Gut Brain Axis** (MGBA) (1).
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– If the Human Genoma Project (HGP) has highlighted that the human body contains approximately twenty-five thousand copies of genes, the Project METAHIT (Metagenomics of the Human Intestinal Tract) allowed to measure the presence of over one million genes belonging to the gut microbiota, capable of influencing a great number of bodily functions.

Based on this close functional relationship, the genetic pool of the microbiome is considered to be strictly correlated to our genetic pool.

The studies conducted within the scope of the METAHIT Project have identified **three different enterotypes** inside the human body (Figure 1) worldwide.

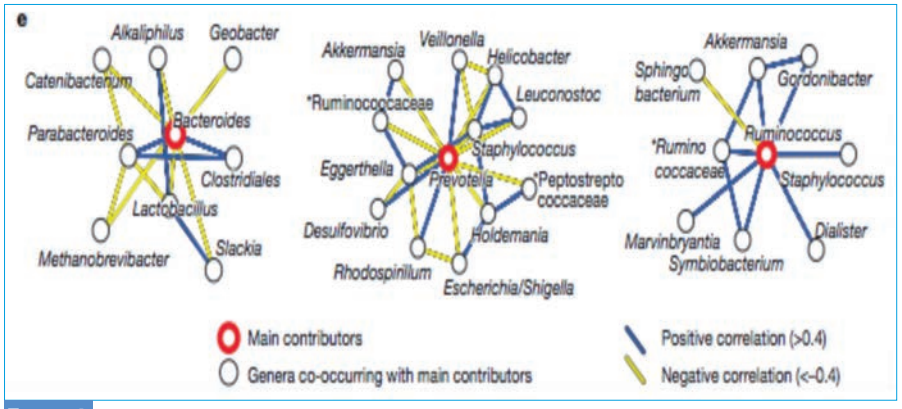

Figure 1

The main microbic components of the three human enterotypes.

Arumugam M., Raes J., Pelletier E., Le Paslier D., Yamada T., Mende D.R. – Enterotypes of the human gut microbiome. Nature, Apr 20, 2011. Vol n 473. Issue n 7346.
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– Each enterotype shows a predominant bacterial genus preferentially associated with some of them rather than others. In this way, a first enterotype can be identified among the **Genus *Bacteroides***, a second enterotype among the **Genus *Prevotella*** and a third enterotype among the **Genus *Ruminococcus*** (2).

The intestinal mucosa is the interface between the microbiota and the organism. On this level much information is exchanged in the intestinal wall thanks to the development of macroscopic and microscopic structures adapted to the interaction between the two partners of the symbiotic relationship.

COMPONENTS OF INNATE IMMUNITY
MECHANICAL FACTORS
Physical epithelial barrier
Tight junctions
Mucus
Peristalsis
BIOCHEMICAL FACTORS
Receptor molecules (PRRs: TLRs - NODs - NLRs)
Peptides for the bacterial killing (defensins, lysozyme, angiogenin, etc.)
Cytokines: link between Innate Immunity and Adaptive Immunity
CELL FACTORS
Epithelial cells
Mast cells
Dendritic cells
NK cells
T lymphocytes
Phagocytes
– macrophages
– granulocytes

Table 1

Components of Innate Immunity.

The special spatial organization of the intestinal wall is mainly based on the self-similarity, thanks to which the wide intestinal surface passes from a macroscopic dimension to a microscopic dimension forming loops, villi and microvilli.
Its surface is approximately **400 mq** of exchange with the intra-intestinal environment, even if it is contained in a much smaller cavity, i.e. the abdominal cavity.

The intestinal mucosa is the interface between the organism, the microbiota and the intraluminal intestinal environment, where a great number of stressors converge.
For this reason, it carries out a complex barrier action that goes beyond a mere selective control action on the transit.

– Therefore, it starts to play an active role in the regulation mechanisms of the MGBA.
In addition to this, since the paracellular and transcellular transit modes influence the type of immune response, they have an impact on the realization of tolerance phenomena or of sensitization of tolerance itself.

In this way, the barrier function of the intestinal mucosa makes the latter an important factor of Innate Immunity, which comprises different mechanical, biochemical and cellular factors (Figure 2).

With the progress of the studies, the role of Innate Immunity (Table 1) in the induction and regulation of adaptive immune response has become increasingly evident. Likewise, its pathogenic and pathophysiological function in a great number of immune and systemic diseases has been better outlined.
Considering the role of the intestinal barrier as part of the innate Immunity, numerous studies have increasingly involved the **alteration of the intestinal permeability** in the onset of these diseases.

– This article intends to focus particularly on two fundamental components of the intestinal barrier and, therefore, on innate Immunity: the **tight junction** and the **Pathogen Recognition Receptors** (PRRs), particularly involved in the pathogenic mechanisms of many intestinal and systemic diseases that imply impaired intestinal permeability as a pathogenic, triggering or concurrent factor.

– The transit of the various substances through the paracellular space between the neighboring intestinal cells is regulated by various junctional systems.
Among these, an important role is played by the **tight junctions**, i.e., junctional structures located in the pre-apical region of the cell.

Their permeability has an extremely complex regulation because there are many factors that can modify it.
– These factors may be related to the different immune, neurological or endocrine structures of the organism, or to the components of the microbiota itself.

– The macromolecular structures that form the tight junctions are closely related to the structures of the cytoskeleton through the intermediary action of the actin filaments (3,4).
This implies that all the active factors that are able to modify the structure of the cytoskeleton, such as NSAIDs and pump inhibitors drugs, may bring about an increase in the permeability

of intercellular junctions, thus altering the function of the intestinal barrier.

The PRRs represent a membrane or cytoplasmic receptor system which allows the cells of the innate Immune System to discriminate between self antigens and non-self microbial antigens, thanks to the recognition of a widely preserved molecular pattern.
Among the most studied and well-known receptors there are the Toll Like Receptors (TLRs), the Nucleotide-binding oligomerization domains (NODs) and the NOD-Like Receptors (NLRs), also known as **Inflammasomes**.

The stimulation of these receptors by the Pathogen-Associated Molecular Patterns (PAMPs), antigens permanently preserved during the evolution of microorganisms, activates the gene transcription of several **pro-inflammatory cytokines** able to stimulate both inflammation and the adaptive immune response.

– The PAMPs include the lipopolysaccharide (LPS) of the wall of the Gram - bacteria, recognized by the TLR4, the peptidoglycan and the lipoteichoic acid of the Gram + bacteria, recognized by the TLR2.

The functional balance of PRRs, especially of the NODs, and the TLRs (5), is essential to preserve the body's healthy conditions, a good protective ability of the intestinal barrier and, therefore, a state of tolerance toward commensal bacteria and food antigens.

Consequently, this also allows to ensure a good antimicrobial activity and a limited bacterial invasiveness.
– The imbalanced relationship between the gut microbiota and mucosal functions alters the function of the PRRs, thus triggering inflammation and destroying the intestinal barrier, which involves a reduced antibacterial action, an increased bacterial invasiveness and a reduced immune tolerance toward food antigens and commensal microorganisms (6).

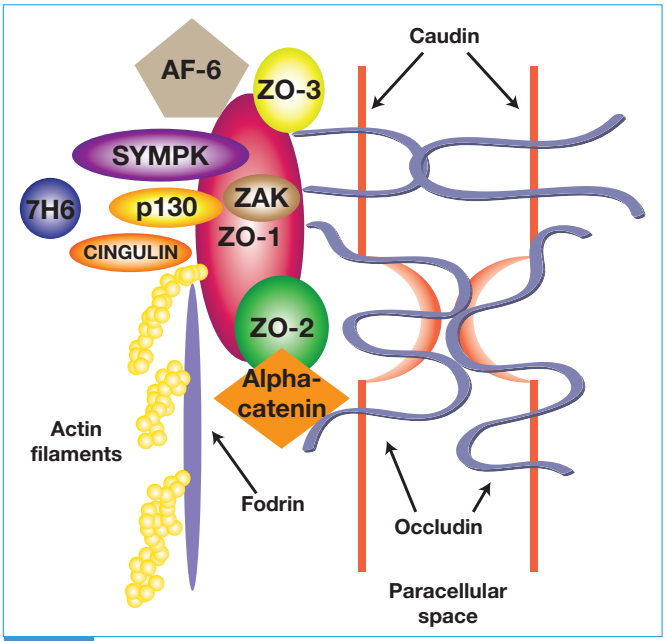

Figure 2

Diagram of the macromolecular structure of the *tight junction*.

The distribution of the PRRs is ubiquitous.
– An altered permeability of the intestinal barrier promotes the passage of the PAMPs through the intestinal wall, both at the level of the gut mucosa and in the lymphatic and portal circulation.
So, at a systemic level, all this induces the appearance of **Low Grade Inflammation** (LGI) in the intestinal wall itself, in the liver (with the appearance of NAFLD) and in different body structures.
This, along with other factors of genetic and epigenetic origin, may be responsible for the onset/worsening of numerous inflammatory and degenerative diseases, in genetically predisposed, autoimmune individuals (7-18).

A clinical history associated with increased permeability is often so complex that it is possible to identify the so-called ***Leaky Gut Syndrome***.

TABLE 2 lists the most common and frequent causes of increased intestinal permeability.
– These causes are very common, frequent and extremely widespread and this also explains the increased incidence of diseases commonly associated with a damaged intestinal barrier.

The condition of LGI, arising from the latter, is considered to be at the basis of different diseases that can range from various **forms of arthritis** to **seropositive and seronegative forms of arthritis**, from **fatty liver disease** (NAFLD) to **metabolic syndromes** associated with **non-alcoholic steatohepatitis** (NASH), from **irritable bowel syndrome** (IBS) to **inflammatory bowel diseases** (IBDs).

At the basis of the different clinical expressivity there is the interaction between genetic and epigenetic factors that, in any case, share an increased intestinal permeability and the resulting LGI.
– Among the most common etiopathogenetic factors underlying the increased intestinal permeability there are stress and the use of NSAIDs more or less associated with PPIs.

Stress causes damage to the intestinal barrier whether the original stressor is "cognitive" or "non-cognitive" (for example the PAMPs themselves).
While the former activates the HPA axis by directly inducing the release of CRH, the latter activates the HPA axis at the level of the innate Immunity cells

MOST FREQUENT CAUSES OF INCREASED INTESTINAL PERMEABILITY

- **Stress**
- **Dysbiosis**
  - Drugs
  - NSAIDs
  - Corticosteroids
  - PPIs
  - Chemotherapy
- **Intestinal infections**
- **High ROS levels**
  - biliary origin
  - foodborne
  - inflammatory cells
- **Intestinal hypoxia**

Table 2

Causes of increased intestinal permeability.

through the production of **IL-1 ß** and **IL-6**, both able to release CRH in the hypothalamus.

Increased cortisol levels, resulting from the activation of the HPA axis, induce a decline in the activity of inflammasomes NLRP3 and NLRP6 (19,20) in the intestinal epithelial cells, which results in a decreased production of IL-1 ß and IL-18.

On the one hand, this leads to the lowering of defensive abilities against the bacterial flora with increased growth of pathogenic bacteria and, therefore, **dysbiosis**; on the other hand, this leads to a **reduced mucosal trophism**.

Dysbiosis, especially in individuals that follow diets rich in saturated fatty acids and animal protein, causes an indirect damage to the intestinal permeability, in relation to the induction of an increased production of secondary bile acids with a decreased production of ursodeoxycholic acid (21), and a direct damage by stimulating the chemokine CCL5, which leads to an increased intestinal permeability through the action on the tight junctions (22).

– The widely used NSAIDs cause significant damage to the intestinal mucosa, inducing an increase of its permeability until the onset of erosive lesions (sometimes ulcerative), through pathogenic mechanisms with a topical and systemic action. Several studies have highlighted the damage produced by some NSAIDs (Figure 3) and, in particular, by indometacin on the intestine of rats.
– Within one hour after administration of the drug, the lab animal shows visible signs of damage to microscopy at the level of the brush border of intestinal cells and mitochondria, which appear swollen and vacuolated.
The systemic mechanism of action is related essentially to the inhibitory action on cyclooxygenase, reducing the regulatory effects of prostaglandins on the intestine (22).
The topical effect is independent of the inhibitory effect on the cyclooxygenase because it is linked to the acidic nature of the NSAIDs and their **uncoupling ability on oxidative phosphorylation**, which results in the alteration of the electron transport in mitochondria (23).

NSAIDs, causing the slowing of mitochondrial respiration (24) through the uncoupling of oxidative phosphorylation, cause damage to the structures of the cytoskeleton and, therefore, to the tight junctions.

– The harmful effects of NSAIDs on the intestinal mucosa are exacerbated when associated with PPIs and are even more severe when combined with low doses of acetylsalicylic acid (25).
The damaging effects of the combination of NSAIDs and PPIs are not only related to the damage caused to the mucosa (membrane damage), but also to the pro-sensitizing and pro-inflammatory action induced by an extremely impaired protein digestion. The PPI causes the block of acid secretion, and so promotes dysbiosis because the gastric acidity does not carry out a protective action against the penetration of pathogenic bacteria introduced orally.
Moreover, it also involves the non-activation of the digestive enzymes that require an acid environment to perform their function.

– This leads to impaired digestion of the proteins that arrive intact in the intestinal lumen.
Because of an increased intestinal permeability produced by the association of NSAIDs with PPIs, these proteins can follow the paracellular pathway until reaching the lamina propria where, after overcoming the barrier, they induce sensitization and inflammation.

Due to the high presence in the population of the causes that bring about the alteration of intestinal permeability and the importance of the latter in the pathogenesis of high incidence diseases, it is necessary to identify therapies that may prevent or cure the alterations of the mucosal barrier.

– Currently there are no drugs on the market that carry out this action.

Physiological Nutraceuticals offer important opportunities, and specifically the association of bovine colostrum with *Morinda citrifolia* (**Colostro Noni**).

Colostrum is the result of the first mammary secretion that is activated immediately after childbirth. It does not contain lactose or proteins such as casein and lactalbumin. Considering that the infant's intestine undergoes a first massive colonization at birth and that it represents the first exogenous trophic and immune stimulus, colostrum is the most comprehensive tool towards (prebiosis) the colonization of the intestine during the final stage of development.

So, it turns out to be useful as a prebiotic in order to recolonize the gut and to prevent and treat increased intestinal permeability.

Due to the essential nourishing action it has to carry out, colostrum is rich in substrates in optimum ratio: vitamins, trace elements, growth factors and hormones, antibodies aimed at encouraging the development of a correct inte-

stinal barrier and the selection of a commensal bacterial flora able to better modulate the Immune System (TABLE 3).

The juice of *Morinda citrifolia* (Noni) has significant anabolic and immunostimulant properties.
The latter would be ascribed, in addition to the same anabolic effect possessed by the plant extracts of its juice, also to deacetylasperulosidic acid.
– The anabolic effects would be induced by the content in proxeronine, xeronine and proxeronase, an enzyme which becomes active in the gut and would turn proxeronine into xeronine, which has important anabolic protein effects on the cells.
The protective effect of colostrum on the intestinal mucosa has been known for some years (26-28).

– The Department of Biomedical Sciences for Health of the University of Milan - Italy has conducted a study to assess the effects of the association colostrum/Noni in an *in vitro* model of intestinal epithelium, both on the growth of enterocytes and on the inductive capacity to release IL8 (29) in order to demonstrate the cytoprotective and immunoregolative properties of colostrum combined with Noni and, therefore, the therapeutic and preventive measures to be taken against membrane damage and impaired membrane permeability.

The study was conducted on Caco2 cells, derived from human colorectal cancer, grown in Dulbecco's Modified Eagle's Medium (DMEM), which, after 21 days after seeding, differentiate into enterocytes, forming an epithelial monolayer with the junctional systems.

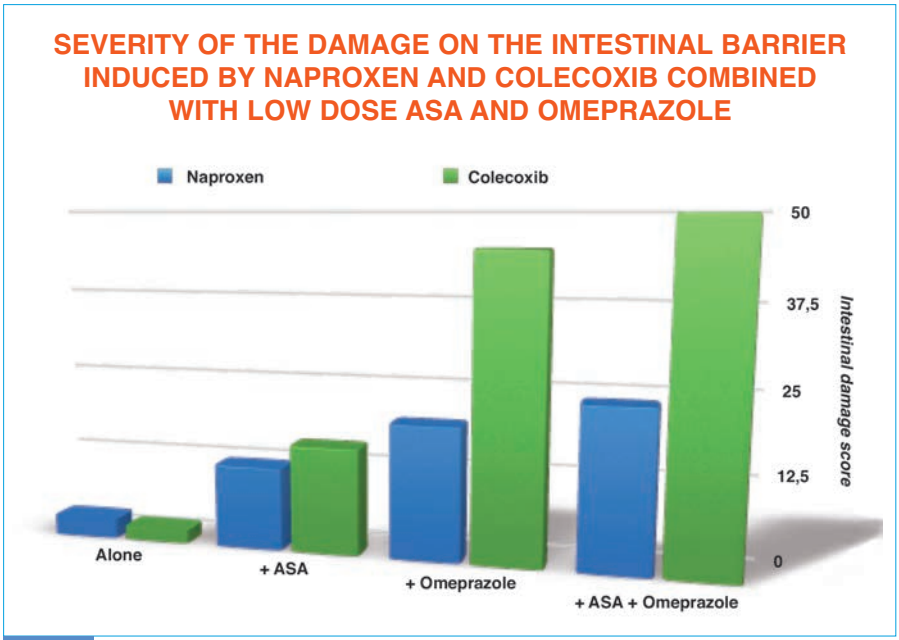

Figure 3

Adverse effects of two NSAIDs (Naproxen and Colecoxib) alone or combined with ASA or/and Omeprazole. The scores are average values.

– *Modified* from Wallas J.L., 2013 (reference 25).

– The study on the evaluation of cell growth showed that a combined treatment of colostrum and Noni positively influences the growth curve, evaluated through WST-1 cell proliferation assay.

The statistical analysis showed that the effect on the increase in the latter was significantly greater when there are both colostrum and Noni in the culture medium (Figure 4a).

IL-8 plays an ambivalent role within the sphere of membrane functions in the intestinal epithelium.

In conditions of eubiosis (30) IL-8 is primarily active on the trophic intestinal mucosa, stimulating angiogenesis, the migration of epithelial cells and helping to restore cell turnover.

When the pathogenic agents stimulate the PRRs, in cases of dysbiosis, the increased production of chemokines and the release of IL-8 in higher doses promotes the chemotactic effect on neutrophils, without causing mucosal damage (31).

– The intervention of other factors will activate granulocytes causing an increase in oxidative stress and, therefore, of inflammation.

Table 3

Main constituents of colostrum.

MAIN CONSTITUENTS OF COLOSTRUM	
Antibodies and immunomodulating agents	IgA/IgM/IgG, high prolin polypeptides, lactoferrin, IL-10, IL-12, glycoproteins and trypsin inhibitors, lymphokines, lysozyme, oligopolysaccharides and glycoconjugates.
Hormones, growth factors, amino acids	Estrogens, androgens, PTH, calcitonin, IGF-1, EGF, FGF, TGF, full amino acid pool.
Vitamins, coenzymes, trace elements	Vitamins A, C, D, E, B group, coenzyme Q10, various trace elements
Minerals	Na, K, Mg, Fe, Cu, Zn, Cr, Se, P, S.

In order to assess the ability of colostrum combined with Noni to stimulate the production of IL-8, the expression of IL-8 (mRNA) has been evaluated in cultured Caco2 cells previously stimulated with TNF-α, a cytokine that stimulate the enterocyte production of interleukin.

The results obtained showed a significant increase of IL-8 (mRNA) especially when the culture medium has been enriched with colostrum and Noni, showing how **the combination of the two nutraceuticals positively influences the gene expression of the cytokine** (Figure 4b).

CONCLUSIONS

We underline the importance of the pathogenic role, confirmed by the increasing number of scientific studies, played by the alterations of intestinal permeability in the onset of important and widespread intestinal and systemic diseases, whose incidence is increasingly high.

This is particularly evident in Western populations where the most common factors responsible for the genesis of the damage to the intestinal barrier are widespread.

Suffice to think of the massive and often uncontrolled use of NSAIDs, their combination with PPIs frequently used for long periods of time, the recurrent, even if not necessary, use of antibiotics and, last but not least, the increase of the stress induced by hectic lifestyles associated with increasingly poor dietary quality.

Some studies carried out on the effects of colostrum and the juice of *Morinda citrifolia* (Noni) on the intestinal mucosa, in relation to the ability to prevent and repair damage to the barrier function of the mucosa itself, have shown the actual efficacy of the combination of the two components.

Therefore, considering that at present there are no drugs able to prevent or cure mucosal damage caused by a great number of frequent iatrogenic and pathogenic factors, the nutraceutical treatment with the **combination of colostrum** and **Noni** is an effective opportunity to prevent and treat any damage to the intestinal barrier caused by dysbiosis.
This damage is due to an increasingly widespread use of NSAIDs, taken alone or combined with pump inhibitors, alcohol abuse, radio-and/or chemotherapy or pathogenic mechanisms triggered by an increased permeability of the intestinal barrier. ■

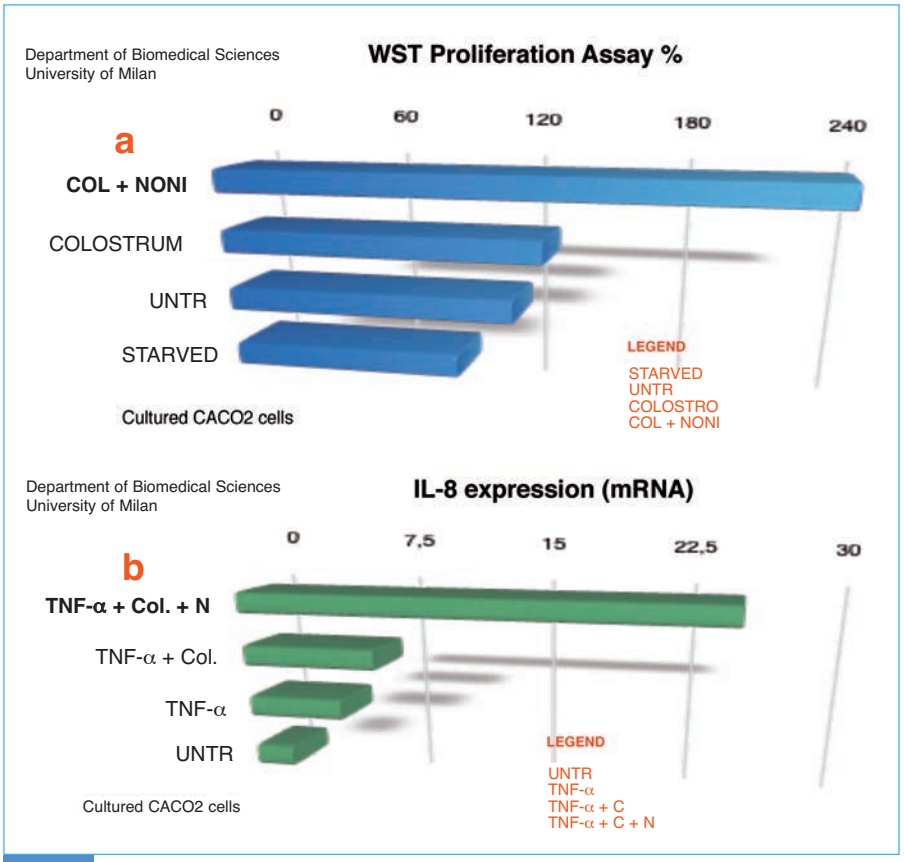

Figure 4

Diagram of the results of the study on the effects of Colostro Noni on an *in vitro* model of intestinal epithelium

a) Effects on cell proliferation in different culture conditions.

b) Effects on IL-8 expression (mRNA) in different culture conditions.

– *Modified from* Cardani D., 2014 (reference 29).

References

1. Rhee S., Pothoulakis C. *and* Mayer E.A. – Principles and clinical implications of the brain–gut–enteric microbiota axis. Nature Reviews Gastroenterology & Hepatology 6, 306-314; **2009**.
2. Arumugam M. *et* Al. – Enterotypes of the human gut microbiome. Nature 473, 174-180; **2011**.
3. Fanning A.S., Mitic L.L. *and* Anderson J. M. – Transmembrane proteins in the tight junction barrier. Journal of the American Society of Nephrology: JASN, 10, 1337-1345; **1999**.
4. Chiba H., Osanai M., Murata M., Kojima T. *and* Sawada, N. – Transmembrane proteins of tight junctions. Biochimica et Biophysica Acta, 1778, 588-600; **2008**.
5. Abreu M.T., Fukata M. *and* Arditi M. – TLR signaling in the gut in health and disease. Journal of Immunology (Baltimore, Md.: 1950), 174, 4453-4460; **2005**.

6. Cario E. – Bacterial interactions with cells of the intestinal mucosa: Toll-like receptors and NOD2. Gut, 54, 1182–1193; **2005**.

7. Picco P., Gattorno M., Marchese N., Vignola S., Sormani M.P., Barabino A., Buoncompagni A. – Increased gut permeability in juvenile chronic arthritides. A multivariate analysis of the diagnostic parameters. Clin Exp Rheumatol. **2000** Nov-Dec;18(6):773-8.

8. Vaile J.H., Meddings J.B., Yacyshyn B.R., Russell A.S., Maksymowych W.P. – Bowel permeability and CD45RO expression on circulating CD20+ B cells in patients with ankylosing spondylitis and their relatives. J Rheumatol. 26(1):128-35; **1999**.

9. Sartor R.B. – Importance of intestinal mucosal immunity and luminal bacterial cell wall polymers in the aetiology of inflammatory joint diseases. Baillieres Clin Rheumatol. 3(2):223-45; **1989**.

10. Faure E. *et* Al. – Bacterial Lipopolysaccharide Activates NF-kB through Toll-like Receptor 4 (TLR-4) in Cultured Human Dermal Endothelial Cells Differential expression of the TLR-4 end TLR-2 in endothelial cells. The Journal of Biological Chemistry Vol. 275, No. 15, Issue of April 14, pp. 11058-11063; **2000**.

11. Linda K., Curtiss L.K. and Tobias P.S. – Emerging role of Toll-like receptors in atherosclerosis. The Journal of Lipid Research, 50, S340-S345; **2009**.

12. Hazenberg M.P., Klasen I.S., Kool J., Ruselervan Embden J.G, Severijnen A.J. – Are intestinal bacteria involved in the etiology of rheumatoid arthritis? Review article. APMIS. 100(1):1-9; **1992**.

13. Ilan Y. – Leaky gut and the liver: a role for bacterial translocation in nonalcoholic steatohepatitis. World J Gastroenterol. 7;18(21): 2609-18; **2012**.

14. Miele L. *et* Al. – Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology. 49(6):1877-87; **2009**.

15. Fasano A. – Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev. 91(1):151-75; **2011**.

16. Vaarala O., Atkinson M.A., Neu J. – The "perfect storm" for type 1 diabetes: the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. Diabetes. 57(10):2555-62; **2006**.

17. Krack A. *et* Al. – The importance of the gastrointestinal system in the pathogenesis of heart failure. Eur Heart J. 26(22):2368-74; **2005**.

18. Mejia J.K. *et* Al. – Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature; 482(7384): 179-185; **2001**.

19. Sun Y. *et* Al. – Stress-Induced Corticotropin-Releasing Hormone-Mediated NLRP6 Inflammasome Inhibition and Transmissible Enteritis in Mice. Gastroenterology. Published online 07 March **2013**.

20. Sun Y. *et* Al. – Stress-Induced Corticotropin-Releasing Hormone-Mediated NLRP6 Inflammasome Inhibition and Transmissible Enteritis in Mice. Gastroenterology. 144, 1478; **2013**.

21. Stenman L.K. *et* Al. – A novel mechanism for gut barrier dysfunction by dietary fat: epithelial disruption by hydrophobic bile acids. Am J Physiol Gastrointest Liver Physiol 304: 227-234; **2013**.

22. Tremaroli V., Bäckhed F. – Functional interactions between the gut microbiota and host metabolism. Nature. doi:10.1038/nature11552; **2012**.

23. Tanaka A., Hase S., Miyazawa T. *and* Takeuchi K. – Up-regulation of cyclooxygenase-2 by inhibition of cyclooxygenase-1: a key to nonsteroidal anti-inflammatory drug-induced intestinal damage. The Journal of Pharmacology and Experimental Therapeutics, 300, 754-761; **2012**.

24. Somasundaram S. *et* Al. – Mitochondrial damage: a possible mechanism of the "topical" phase of NSAID induced injury to the rat intestine. Gut 41;344-353; **1997**.

25. Wallas J.L. – Mechanisms, prevention and clinical implications of nonsteroidal anti-inflammatory drug-enteropathy. World J Gastroenterol. 19(12): 1861-1876; **2013**.

26. Uruakpa F.O., Ismond M.A.H. *and* Akobundu E.N.T. – Colostrum and its benefits: A review. Nutrition Research. doi:10.1016/S0271-5317(02)00373-1; **2002**.

27. Playford R.J. *et* Al. – Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders. American Journal of Clinical Nutrition Vol.72, No.1, 5-14; **2000**.

28. Thapa B.R. – Health factors in colostrum. Indian Journal of Pediatrics, 72, 579-581; **2005**.

29. Cardani D. – Effetti di Colostro Noni sul turnover delle cellule epiteliali, sugli stati infiammatori e sull'integrità dei sistemi giunzionali della mucosa intestinale. Minerva Gastroenterol. Dietol., Vol. 60 N.1; **2014**; 71-8.

30. Wilson A.J., Byron K., Gibson P.R. – Interleukin-8 stimulates the migration of human colonic epithelial cells in vitro. Clinical science 97, 385-90; **1999**.

31. Kucharzik T., Hudson J.T., Lügering A., Abbas J.A., Bettini M., Lake J.G., Williams I.R. – Acute induction of human IL-8 production by intestinal epithelium triggers neutrophil infiltration without mucosal injury. Gut, 54, 1565-1572; **2005**.

author

Dr. Enrico Biffi

– Specialist in General Surgery

Via Niccolò Tommaseo, 2

25128 Brescia, Italy