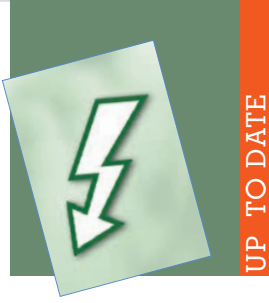


D. Cardani



## SUMMARY

The gastrointestinal tract takes part of a complex network, which includes the Central Nervous System and the intestinal microbiota, known as Microbiota-Gut-Brain Axis playing a central role in the whole body homeostatic control. The Microbiota-Gut-Brain Axis is part of the fundamental Psycho-Neuro-Endocrine-Immune homeostatic network. The intestinal homeostasis is therefore based on a delicate balance, called physiological inflammation, established between gut microbiota and the intestinal immune system. A large number of pro-inflammatory triggers, especially an unhealthy diet, could affect the delicate homeostatic balance between epithelium barrier function, microbiota and immune response. A correct dietary supplementation may represent an important approach in order to reduce inflammatory triggers effects on intestinal homeostasis. Alimentary supplements containing Bovine Colostrum and Noni Juice show the ability to enhance cellular turnover and cell migration at intestinal epithelium level exerting a well-documented protective activity. Bovine colostrum-derived lactoferrin and polysaccharidic fraction contained in both colostrum and Noni juice exerts a key action for intestinal homeostasis maintenance modulating both immune response and enterocytes proliferation, fundamental mechanisms for both early developmental and continuous self-renewal intestinal processes; the stimulation of these cellular pathways is the key concept to understand the role of bovine colostrum and Noni juice in a dietary supplement formulation. Enterocytes internalize bovine lactoferrin by a specific carrier. Lactoferrin activates ERK1/2-mediated cellular pathways involved in proliferation, migration, and cell differentiation processes. Polysaccharide-rich fractions of colostrum and Noni juice are able to modulate cellular response mediated by Toll-like R; well-grounded literature data show how plant-derived polysaccharides are immunomodulatory agents and as this control action is mediated by Toll-like Receptors, through a signal cascade involving PI3K/Akt/MAPKs and leading to nuclear translocation of NF- $\kappa$ B. Enhanced IL-8-expression mediated by Toll-like receptors and NF- $\kappa$ B generates an autocrine loop which regulates the mechanisms of re-epithelialization that follows a structural alteration of the epithelium induced by an inflammatory trigger. If it is not possible to follow an op-

## NEW PERSPECTIVE IN DIETARY SUPPLEMENTATION: BOVINE COLOSTRUM AND NONI JUICE SYNERGIC PROTECTIVE EFFECTS ON INTESTINAL EPITHELIUM AND MICROBIOTA

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### CENTRAL ROLE OF INTESTINE FOR WHOLE BODY HOMEOSTASIS

The gastrointestinal tract is the largest communication interface of the human organism with the external environment, covering about 300 m<sup>2</sup> of exposed surface area (1).

The function of physical separation between the intestinal lumen and the underlying tissues of the gastrointestinal tract is committed to the intestinal mucosal layer; enterocytes, enteroendocrine cells, goblet cells, Paneth's cells and immune cells are the main components of the intestinal epithelium.

The structural cohesion of this monolayer is the precondition that underpins an optimal barrier function exerted from

intestinal mucosa (2).

Recently, the gastrointestinal tract acquired a significance that goes beyond its specific functions of being a dynamic protective barrier and a selective digestive filter: it takes part of a more complex network which includes Central Nervous System (CNS) and intestinal microbiota; this network is known as Microbiota-Gut-Brain Axis (MGBA) and plays a pivotal role in the homeostatic control for the entire body (3-5).

The MGBA integrated communication system is one of the fundamental Psycho-Neuro-Endocrine-Immune (PNEI) mechanisms of homeostatic control (4, 6, 7).

Between the CNS, the gut and its microbiota a continuous psychoneuroendocrine cross-talk exists, based on different kinds of signal molecules: CNS

timial diet, proper integration based on the use of dietary supplements containing bovine colostrum and Noni juice can be an effective strategy for the prevention of intestinal LGCI states and, consequently, to reduce the chances of developing inflammatory-based chronic systemic diseases.

### KEY WORDS

BOVINE COLOSTRUM, NONI JUICE, IL-8, CXCR1, TOLL-LIKE RECEPTORS, BOVINE LACTOFERRIN, LFR, POLYSACCHARIDES, INTESTINAL EPITHELIUM, MICROBIOTA.

communicates with the intestine and the microbiota through neurotransmitters and hormones like corticotrophin releasing hormone (CRH), managing some parameters such as epithelial permeability (controlled by the modulation of Junctional Systems) and microbiota composition (8, 9). On the other hand, the gut and the microbiota interact with the CNS through the production of metabolites such as tryptophan that is recognized at the central level of influencing brain and behavior (4); the gut is unequivocally a psychoneuroendocrine organ.

About 70% of immunocompetent cells is localized into the intestinal mucosa (GALT) and represents the largest immunocompetent organ of the entire body (10) showing a central role as the Immune component of PNEI axis (11).

GALT exerts two main functions, in partial contradiction between them: (I) to ensure optimal protection against potential pathogens and, at the same time, (II) to avoid exaggerated responses against innocuous antigens originating from the commensal flora or food; these two functions are part of the mechanism known as immunotolerance (12, 14). Dendritic Cells (DC) located in the Peyer's patches are able to ensure continuous monitoring of the antigens located on the surface of the intestinal epithelium or in the mucous layer, contributing to immunotolerance management (14, 15).

The intestinal PNEI homeostasis is therefore based on a delicate balance established, under physiological conditions, between the intestinal microbiota and the GALT; this balance is represented by the persistence of a physiological or "controlled" inflammation (4).

The intestinal epithelium represents the battlefield of immunotolerance and its integrity is a fundamental prerequisite for homeostasis maintenance. In presence of structural or functional epithelial alterations (such as mucosal lesions or impaired permeability conditions)

the stable environment between the gut and the microbiota is altered (16) and GALT-mediated immunotolerance is compromised: this imbalance leads transition from controlled inflammation to Low Grade Chronic Inflammation (LGCI) (17, 18), a sub-acute inflammatory condition underpinning a great number of chronic diseases (19, 20). It is therefore clear that maintenance of epithelium integrity is essential for the explanation of active and passive defense against both endogenous and exogenous inflammatory triggers and for the maintenance of MGBA homeostasis through an efficacious control of mucosal self-renewal mechanisms and epithelial permeability.

Cell turnover is a fundamental mechanism for the regeneration of labile tissues such as epithelia. Compared to all other tissues, epithelium of the gut appears to be the fastest to regenerate. In fact, intestinal epithelium is completely renewed in about three days.

Under physiological conditions, the intestinal mucosa maintains its structural homeostasis, balancing the factors that induce programmed cell death, and that underpin the processes of cell replacement (21). In presence of epithelial lesions the mucosal repair is based on two complementary mechanisms: the first rapid response consists in the stimulation of the migration of still viable cells in the injured area (mucosal restitution) while the second, slower, is the active restoration of the damaged area by enhanced cell division (22).

Physiological cell proliferation, cell migration and management of Junctional Systems are therefore fundamental to the establishment of the mechanisms of mucosal repair and epithelial permeability maintenance.

## HOMEOSTASIS DISRUPTION: INFLAMMATORY TRIGGERS AND INTESTINAL EPITHELIAL INTEGRITY

The delicate homeostatic balance between the epithelium's dynamic barrier function, intestinal microbiota and immune response, all of controlled by physiological inflammation, may be adversely affected by a large number of pro-inflammatory triggers including infections, chronic stress, incorrect lifestyle, prolonged or incorrect drugs therapies and, especially, an unhealthy diet (23-25).

Gut microbiota and intestinal epithelium are severely affected by the action of pro-inflammatory triggers: the microbiota can be destroyed or altered in its qualitative and quantitative composition and the intestinal epithelium can lose its integrity and permeability. The most common cause of intestinal homeostasis alteration remains an incorrect diet; it is in fact proven that some nutrients are able to modulate either positively (for example antioxidants such as vitamins C and E) or negatively (for example, fatty acids in excessive amount) the functionality of the intestinal barrier by modulating TJ opening, mucus production and epithelial cells turnover.

The so called "Western Diet" (WD) (26) is particularly rich in fats and sugars and it is mainly composed of highly transformed foods with a frequent presence of raw materials derived from genetically-modified organisms (GMO). Long-term WD intake negatively influences intestinal barrier function and contributes to a radical change in microbiota composition; these perturbing events are considered essential risk factors for the development of chronic inflammatory diseases including Crohn's Disease (CD), IBDs, Leaky Gut Syndrome and metabolic diseases such as Type II Diabetes and Obesity (26, 27).

A correct dietary supplementation may represent an important approach in order to reduce inflammatory triggers effects on intestinal homeostasis.

## DIETARY SUPPLEMENTATION: PROTECTION AND RESTORATION OF INTESTINAL MICROBIOTA AND EPITHELIUM

In 1907 Elie Metchnikoff published "The prolongation of life: optimistic studies" introducing for the first time the concept of probiotics, defined as living micro-organisms by Guarner *et Al.* in 1998 (28). In the last decade the concept of probiotics as "immune modulator agents" was introduced (29, 30) explaining the relationship between probiotics and GALT based on the fundamental concept that intestinal epithelium and microbiota represent a functional unit able to regulate both cell-mediated and innate immunity. Recently, the deeper comprehension of the close relationship between the gut and its microbiota led scientists to use the term "human superorganism" (31) in order to describe this mutualistic link; probiotics and prebiotics gradually increased in importance as a functional component of a healthy diet-style. Increasing scientific evidence assessed their beneficial effects at a gastrointestinal level (32, 33): probiotics exert a key role for the maintenance of the superorganism homeostasis rebalancing and/or restoring the qualitative/quantitative ratio among the different bacterial strains within microbiota.

From a PNEI point of view, another cardinal point for intestinal homeostasis management is represented by the protection or the restoration of a healthy epithelial monolayer which is essential for correct microbiota modulation inside the MGBA axis.

In this field, alimentary supplements containing Bovine Colostrum (BC) and Noni Juice (NJ) (34), occupies a peculiar functional niche showing the ability to manage the two main aspects of epithelial mucosal repair mechanisms: enhancement of cellular turnover and cell migration, in fact BC and NJ exert well-documented actions in terms of immunomodulation and epithelial protection/restoration.

## BOVINE COLOSTRUM: A NATURAL IMMUNOMODULATING AND PROTECTIVE AGENT

**Colostrum** is the first milk produced by mammals 24-48 hours after birth.

Compared to "mature" milk, colostrum has a specific nutritional profile and immunological characteristics: it contains growth factors, peptides with antibacterial properties, oligosaccharides and immunologically active substances that are absent (or detected only as traces) in regular milk (35).

Bovine Colostrum (BC) plays the physiological function of stimulating the formation of the intestinal epithelium through a double mechanism of cell proliferation and differentiation. The complex and rich composition of colostrum makes it difficult to describe several of the cellular mechanisms that are activated by the colostrum itself; however, some key steps involving the oligosaccharide components and the protein Lactoferrin are described, based upon the interaction of these components with specific receptors expressed by intestinal epithelial cells (36-38).

Lactoferrin is one of the most important proteic constituents, involved in intestinal epithelial development and immune response enhancement (39). Lactoferrin is a glycoprotein that is able to promote enterocytes proliferation and differentiation in a concentration-dependent manner: high concentrations of Lactoferrin induce a significant proliferation of intestinal epithelial cells while low concentrations stimulate cell differentiation (40).

Lactoferrin is instead internalized by endocytosis from the cell via a specific receptor named LfR expressed on the enterocytes apical membrane. The internalized complex lactoferrin-LfR induces the proliferation of epithelial cells through the activation of the signal cascade mediated by Ras-ERK1/2 (extracellular signal-regulated kinase 1/2; two proteins of MAP-kinase family involved in the regulation of the cell cycle, in particular meiosis, mitosis and post-mi-

totic functions) (41, 42); ERK1/2 signaling cascade is also implicated in the induction and secretion of the antimicrobial peptide  $\beta$ -defensin-2 in intestinal epithelial cells (43).

Oligosaccharides contained in BC mimic the typical Toll-Like Receptors (TLRs) -2 and 4 ligands; the activation of these receptors, as already mentioned, is linked with the increase in the cytotoxicity of NK cells (44). The increased activity of NK cells is closely related to the improved ability of defense against viral infections. The loss of body weight due to the progress of the viral infection is an indirect parameter for the assessment of the integrity of the intestinal epithelium. Increased permeability is often associated with inflammatory phenomenon consequent to infection; BC assumption significantly reduces infection-associated weight reduction protecting epithelial integrity.

Therefore, lactoferrin and other BC components play a fundamental action for iron absorption, intestinal immune response and cellular proliferation, which are fundamental mechanisms for both early developmental and continuous self-renewal intestinal processes; the stimulation of these cellular pathways is the key concept to understand the role of BC in dietary supplement formulation (34).

## NONI JUICE: FROM ANCIENT TRADITIONS, A POWERFUL NATURAL PHYTOTHERAPIC RESOURCE

The plant *Morinda citrifolia* L. (Noni) (Figure 1) has been known by Polynesian people for approximately 2000 years and used for food, textile industry (dyes) and in traditional medicine. All parts of the plant are used, from the roots to the leaves and fruits; Noni juice (NJ) is extracted from the fruit pulp. It is essential in traditional pharmaceutical preparations used for anti-inflammatory and an-



Figure 1

**Morinda citrifolia L. fruit.**  
[https://upload.wikimedia.org/wikipedia/commons/3/3a/Noni\\_fruits\\_and\\_flowers\\_%28Morinda\\_citrifolia%29.JPG](https://upload.wikimedia.org/wikipedia/commons/3/3a/Noni_fruits_and_flowers_%28Morinda_citrifolia%29.JPG)

tiviral purposes, and for regulation of metabolism. The most important compounds identified in NJ are polysaccharide phenolic compounds, vitamins, organic acids, minerals and amino acids. Another alkaloid compound named xeronine has been identified, but its chemical structure is unknown (45-47).

In regards to the biological activity of NJ, its immunomodulatory properties are particularly important; the polysaccharide fraction of NJ is able to modulate cellular response mediated by TLRs, in particular TLR-3, 4 and 5, in a dose-

dependent manner (48). Numerous literature data show how plant-derived polysaccharides are immunomodulatory agents (49-51) and this control action is mediated by TLR-4, in particular through the signal cascade that involves PI3K/Akt/MAPKs and leading to nuclear translocation of NF-κB.

NJ is able to induce an increased expression of the receptor TLR-4 in a dose-dependent manner (48) and the polysaccharides contained in it bind to the receptor on the cell surface inducing the nuclear translocation of NF-κB with consequent production of cytokines and chemokines, including IL-8 and IL-12 (48). NJ enhances TLR-4 activity inducing antiviral and antibacterial responses mediated by IL-8 and IL-12; however, IL-8 also has an autocrine function at the epithelial level (52, 53).

### HYPOTHETICAL MECHANISM FOR BC AND NJ SYNERGIC PROTECTIVE ACTIVITY

Substantial evidences from literature show that BC and NJ exert regulatory effects on the immune homeostasis mechanisms interacting with the gastrointestinal tract.

Bovine Lactoferrin (bLf) contained in BC has a fundamental action on the formation of the intestinal epithelium (43); bLf is internalized by enterocytes after binding to the specific receptor/transporter LFR (41, 42); the result of this event is the activation of cellular pathways involved in proliferation, migration, and cell differentiation processes. The pivotal point of this signal downstream is the activation of specific genes induced by ERK1/2 (41, 42).

Oligosaccharidic fraction is a relevant component of BC (43): oligosaccharides are known to be able to act as ligands for two important receptors, TLR-2 and 4, and are expressed on the apical membrane of the enterocytes; they participate in the innate immune response (immune tolerance) acting like sensors for the detection of pathogens in the intestinal lumen. The pivotal point of the signal cascade following their activation is the nuclear translocation of NF-κB, a key factor for the initiation of numerous physiological functions of the cell, including cell proliferation and differentiation and inflammatory response (54). Even the polysaccharide fraction of NJ has revealed the ability to increase both the gene expression of TLRs cited and their activation, assessed in terms of production of IL-8 (CXCL8), which is a cytokine key to several cellular processes (48, 55).

The induction of IL-8-mediated pathway controlled by TLR-2/4/NF-κB is the focal point for the understanding of the synergistic effect of BC and NJ.

IL-8 has the essential feature to perform different functions depending on the intensity with which it is expressed and depending on the cellular localization of issue: epithelial concentrations in a range of 3-500 pg/ml (49) are related

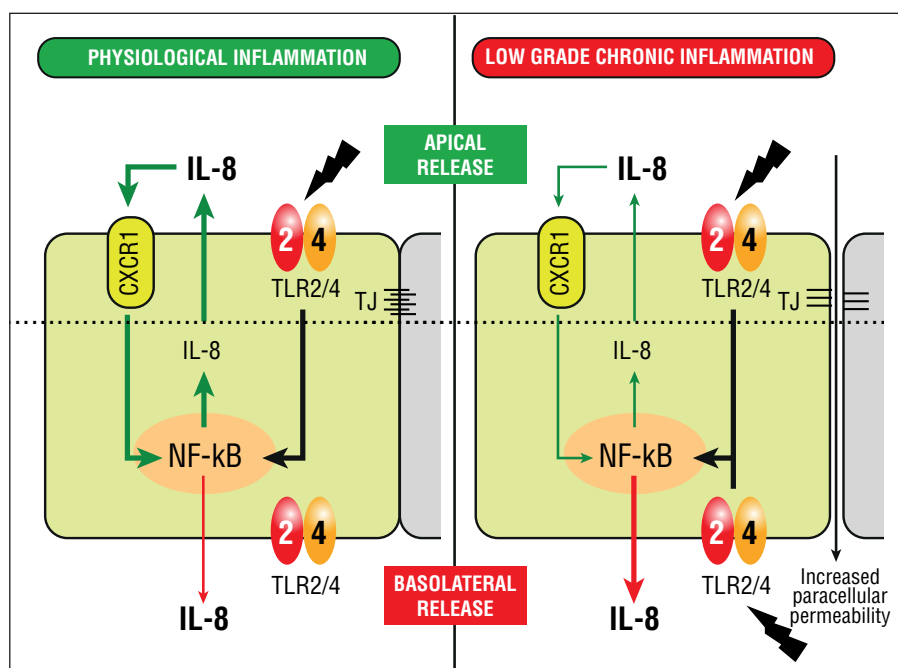


Figure 2

**Graphic representation of IL-8 differential release.**

**In physiological conditions IL-8 autocrine loop sustains epithelial healing processes; in presence of LGCI increased IL-8 basalateral release enhances inflammation acting as chemotactic factor for immune cells.**

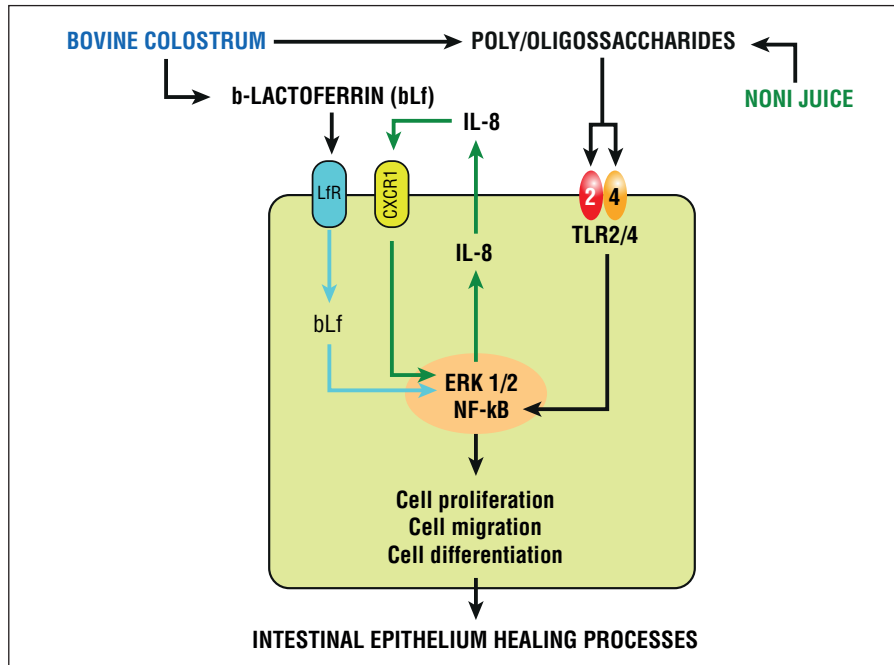


Figure 3

**Hypothetical intracellular pathway describing synergistic protective effects of BC and NJ. Bovine lactoferrin and oligosaccharides fractions sustain IL-8 autocrine loop enhancing ERK 1/2- and NF-kB-mediated physiological epithelial healing processes.**

with the autocrine loop of regulation of mechanisms re-epithelialization that follows the structural alteration of the epithelium induced by an inflammatory trigger. In contrast, higher concentrations (in a range of 3-4000 pg/ml) (56) induce dysregulation of epithelial Junctional Systems (particularly Tight Junctions - TJ) resulting in a loss of cohesion of the epithelium itself with increased paracellular permeability; these findings describe a substantial concentration-dependent biphasic effect of IL-8 at the epithelial level.

Another fundamental parameter involved in differential response to IL-8 production is the localization of the release of IL-8 by the epithelial cell. The basolateral release of large amounts of IL-8 induces the initiation of the inflammatory response (chemotaxis of immune cells and TJ alteration) while the release position apical of limited quantities of IL-8 has an autocrine function primarily mediated by the membrane receptor CXCR1, expressed only in the apical portion (Figure 2).

The IL-8 autocrine loop is essential for the induction of re-epithelialization phenomena mediated by the kinase ERK1/2 (49, 55, 57); therefore, it could be hypothesized that the trigger of the autocrine loop of IL-8 through the

physiological stimulation of the cytokine itself carried by BC and NJ is essential for the synergistic support of the effect on the cell turnover exerted by bLf (Figure 3).

### CONCLUSIONS: "TAKE CARE OF YOUR GUT" AS A NEW PARADIGM FOR THE MAINTENANCE OF THE BODY'S HOMEOSTASIS

Mucous layer, intestinal microbiota, TJ and GALT represent the four basic levels of the intestinal barrier. The gastrointestinal tract is also configured as a PNEI system contributing decisively to control both local and systemic physiological homeostasis: the gastro-intestinal tract represents a neuro-immune-endocrine microcosm with its own crucial role in the homeostatic control. Acting at the level of the gastro-intestinal tract is the key to prevent or to treat both systemic and local pathological alterations, restoring or preserving its histological integrity and its homeostatic PNEI controller function.

Assuming that the human organism is actually a superorganism, it is easy to

understand how the intestinal structure and function are closely dependent on the relationship between microbiota and PNEI axis; their interdependence ensures the integrity of the mucosa and ensures the maintenance of that state of inflammation "physiological" or "controlled", which is fundamental to ensure immune tolerance. The disruption of the balance between neuro-immune-endocrine control function and composition of the mucosal microbiota is the basis of the shift between physiological inflammation and LGCI, the trigger of numerous gastro-intestinal and extra-intestinal diseases.

Today we know that a lot of overlap between the microbiota and function PNEI is mediated by the MGBA axis: alteration of the physiological composition of the microbiota, induced by psychological stress that is transmitted along the MGBA axis, results in loss of its controller role of inflammatory homeostasis, with consequent increased LGCI.

It is easy to understand, therefore, how the alteration of the MGBA homeostasis is a fundamental event in the onset of diseases with a strong psychosomatic component such as, for example, IBS (a disease with high incidence in most industrialized countries, affecting about 15% of the population) (58, 59). Changes in the function of MGBA are also present in diseases such as CD (affects between 27 and 48 per 100,000 inhabitants) and other acute and chronic diseases (with high incidence in Western countries). These changes turn out to be one of the most significant consequences of an unhealthy diet/lifestyle (alcohol and tobacco abuse and/or "junk food" consumption).

All of these diseases recognize inflammatory etiology, supported by a signifi-

cant modification of the intestinal barrier and in particular TJ alteration; various therapeutic strategies are available to manage pathological alterations of the intestinal barrier but a healthy diet represents the initial and most important approach in order to restore or preserve intestinal homeostasis (60- 62).

If it is not possible to follow an optimal diet, proper integration based on the use of dietary supplements containing BC and NJ, which show modulating properties in relation to the key processes of epithelium repair and protection, can be an effective strategy for the prevention of intestinal LGCI states and, consequently, to reduce the chances of developing inflammatory-based chronic systemic diseases. ■

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