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THE ROLE OF GUT MICROBIOTA IN COMPLEMENTARY AND INTEGRATIVE MEDICINE: ON BEHALF OF THE INTEGRATIVE MEDICINE RESEARCH GROUP (IMRG)

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Abstract – The Integrative Medicine Research Group (IMRG) presents here a new conference scene on the role of gut microbiota in complementary and integrative medicine.
The history of microbes in human dates back to the beginning of time; however, the first visual demonstration of a microorganism occurred in 1674. In fact, no one at that time would have ever imagined that microorganisms are crucial for our life and survival. Today we know that microorganisms interact with our body and are called microbiota. Their genome expression is called microbiome. Recently, thanks to extensive research regarding human microbiota in health and diseases, new medical and laboratory technologies have played a crucial role in understanding more complex biological pathways between human cells and microbes. The aim of this conference was to explain the relationship between the human gut and its microbiota in the complex scenario of complementary and integrative medicine.

Keywords: Chronic disease, Patients, Microbiota, Integrative medicine.

INTRODUCTION

The aim of this conference scene, produced by the Integrative Medicine Research Group (IMRG) in Italy, is to focus on the role of human gut microbiota in the context of integrative medicine.

According to the National Cancer Institute, integrative medicine is an approach to medical care that combines standard medicine with Complementary and Alternative Medicine (CAM) practices, that have been shown in scientific research to be safe and effective. This approach often stresses the patient's preferences, and it attempts to address the mental, physical, and spiritual health aspects[1].

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In this context the human gut microbiota plays a crucial role due to its interactions with many aspects of our life, health and diseases[2].

The first evidence of interaction between microbes and human dates back to the early 20th century when Elie Metchnikoff observed that Bulgarian people, who were accustomed to drinking fermented milk, exhibited a higher life expectancy. This is indeed how we moved from the single germ theory and Koch's postulates to the multiple-germ model, in which eubiosis or dysbiosis may correspond to health or disease[2].

Recently, thanks to extensive research regarding human microbiota, health and diseases, new medical and laboratory technologies have played a crucial role in understanding more complex biological pathways between human cells and microbes.

Now the multiple activities of microbiota and its interaction with our body has been fully demonstrated, and it is implicated in obesity, dysmetabolic disease, chronic diseases, cancer, immunomodulation activity, etc[3-5]. Here, we highlight the most relevant presentations given by speakers at the conference on the "Role of gut microbiota in complementary and integrative medicine", with the aim to improve knowledge on this topic using a multidisciplinary approach, including integrative medicine.

ORAL SESSION

Gut Microbiota: The Importance of Prebiotics and Fibers in Reducing Inflammatory Processes

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Human and microbiota share a symbiotic relationship in which the health of both parties is the final goal. In this complex relationship, gut microbiota constitutes the majority of the bacterial biomass and can affect eubiosis or dysbiosis with repercussions on different organs. More specific investigations carried out using 16s rRNA sequencing techniques made it possible to identify the most common bacterial phyla: Firmicutes and Bacteroidetes constitute up to 90%, whereas Actinobacteria, Proteobacteria, Fusobacteria, Cyanobacteria and Verrucomicrobia represent the remaining 10%. In this mutualistic symbiosis, the main advantages that microorganisms derive from humans are the maintenance of a stable temperature, an anaerobiotic environment and a supply of nutrients. The advantages conferred from the gut biomass to the human body are metabolic and structural, especially for the maintenance of the integrity of the intestinal and blood brain barrier, and immune, for protection against common pathogens[6]. In adults the microbiota fluctuates around a steady state in terms of composition, richness and biodiversity and it remains resilient, unless major changes occur.

Dysbiosis is not only defined by an altered gut composition, but rather by the loss of microbiota stability as shown by a different gut microbiota composition compared to the mean normal composition[7]. In this context, soluble fibers in the diet represent a fundamental element for improving the robustness and biodiversity of microbiota, as they are actively used as microbiota-accessible carbohydrates (MAC). MAC are necessary for the production of short-chain fatty acids (SCFA), such as propionate, butyrate, acetate and lactate, which exert a trophic action on the mucosa, as well as anti-inflammatory and local and systemic immunomodulating effects[8]. Diet therefore plays a fundamental role in the modulation of microbiota biodiversity.

When the biodiversity of the gut microbiota is poor, such as in people who follow a Western diet, the intake of a large quantity of fiber can produce gastrointestinal (GI) symptoms. This happens because only a small amount of fiber is efficiently metabolized. In this case a gradual introduction of fibers in a starving diet is needed in order to avoid GI symptoms. Furthermore, a diet rich in MAC is associated with a decrease in the onset of age-related, chronic, degenerative conditions, such as irritable bowel disease, type 2 diabetes, cardiovascular disease, cancer and neurodegenerative conditions[9,10]. Mediterranean diet and its richness in vegetables, fruit, cereals, unsaturated fats, fish, nuts and pulses, with a low content of saturated fats and sugar and a moderate wine and dairy intake, guarantee the best microbiota biodiversity. Mediterranean diet, in particular, increases Bifidobacteria which are associated with longevity, and Lactobacilli, both producers of SCFAs and precious allies of our health.

Restoration and Maintenance of Intestinal Mucosa Integrity with Phytosomates Nutraceuticals

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Inflammatory bowel diseases (IBDs) represent one of the most common classes of diseases in modern society. IBDs are strictly related to colon and small intestine inflammatory conditions.

Curcuma longa L. rhizome and *Boswellia serrata* gum resin are the most promising phytotherapeutic treatments for IBDs[11,12]. It is already known that *Curcuma longa* root has traditionally been used in clinical therapy for alleviation of gastrointestinal disorders. Several studies reported that curcuminoids have anti-inflammatory and antioxidant activities. Molecular mechanisms underlying these properties include the inhibition of NF-κB, cyclooxygenase, and lipoxygenase pathways, as well as the decrease in reactive oxygen species (ROS) production[13]. *Boswellia serrata* exerts its antioxidant and intestinal anti-inflammatory activities through inhibition of lipid peroxidation and enhancing levels of superoxide dismutase[14,15]. This work demonstrated that the combination of dry extracts of *Curcuma longa* L. rhizome and *Boswellia serrata* gum resin could represent a promising treatment for IBDs. The combination of these natural compounds results in an efficient maintenance of the integrity of the intestinal barrier, even under the inflammatory stimulus. In addition, the evaluation of cytokines and ROS production levels in human epithelial colorectal cells and in immune cells confirmed the involvement of these natural drugs in cellular inflammatory responses, as well as the capability to localize in tight junctions and confer barrier resistance.

The Prebiotic Action of Nutraceuticals, from Mucosal Anti-Inflammatory Activity to Liver Detoxification

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In recent years, a new field of research has been developing, with nutraceutical and phytotherapeutic remedies and in improving conditions of dysbiosis through their prebiotic, anti-infective and anti-inflammatory action on intestinal mucosa. Furthermore, studies have investigated how a condition of intestinal dysbiosis can interfere with the mechanisms of liver detoxification and how various remedies useful for improving liver detoxification have also proven useful to restore a correct functioning of the microbiota, establishing a link between intestinal and liver health. The liver and the gut should always be considered and treated together regardless of the pathology requiring an intervention. Generally, to restore a correctly functioning microbiota it is necessary to initially reduce the potentially pathogenic bacteria and phytotherapy offers very important remedies, such as essential oils (EO). Aromatherapy, i.e., the science of EOs, has a major impact on intestinal dysmicrobism. Until a few years ago, however, the use of these remedies was scarce, due to the lack of knowledge of the chemotypes present in the remedy. Recent studies on animals have shown that some EOs, such as *Origanum vulgare*, decrease endotoxin levels in serum, and increase the height of the villi and the expression of occludin and zonula occludens-1 (ZO-1). These studies have shown that EOs restore the integrity of the intestinal barrier compared to the control group[16]. Furthermore, the animals treated with EOs had a lower prevalence of *Escherichia coli* in the jejunum, ileum and colon compared to the controls. Finally, inflammation was also reduced, as suggested by the signaling pathways of mitogen-activated protein kinase (MAPK), protein kinase B (Akt), nuclear factor κB (NF-κB) and cytokine inflammatory expression during fasting.

Use of EOs can also act as an *Add on Therapy* in case of the use of synthetic antibiotics, reducing the phenomenon of antibiotic resistance, since EOs have a strong potential for direct killing, reducing bacterial antibiotic resistance.

Numerous nutraceuticals and phytotherapeutic remedies, such as *Curcuma longa, Boswellia serrata, Zingiber officinalis, Camelia sinensis, Silymarima*, zinc and N-acetylcysteine demonstrated a prebiotic action. As a matter of fact they increase *Bifidobacterium, Alloprevotella* and *Allobaculum* bacterial species, among the larger Short Chain Fatty Acids producers. These nutraceuticals and phytotherapeutic remedies improve alpha diversity, also in co-administration with antibiotic therapy[17], and at the gender level, decrease the prevalence of *E. coli, Shigella* and *Bacteroides* species. Furthermore, it has been shown that these changes coincide with the moderate restoration of the intestinal barrier function, in particular the restoration of the tight junction protein ZO-1, thus having a prebiotic, anti-infective and tight junction-enhancing action[18].

Some studies[19-21] reported that curcumin and green tea epigallocatechin gallate increase the levels of *Akkermansia muciniphila*, essential bacteria for intestinal membrane repair, reduction of endotoxemia, increase in SCFA and relevant in reducing metabolic syndrome related complications. Curcumin also increased the levels of another important bacterium, *Faecalibacterium prausnitzii*, an important producer of butyrate, which reduces intestinal permeability and has an anti-inflammatory activity[22].

N-acetylcysteine is an essential amino acid useful for liver detoxification and a precursor of glutathione. It allows the modulation of the inflammation induced by lipopolysaccharides (LPS) of Gram-negative bacteria, and the reduction of levels of trimethylamine N-oxide (TMAO), a biologically active molecule generated by the intestinal microbiota. A few studies[23,24] have shown a close association between high plasma TMAO levels and the increasing risk of developing atherosclerosis.

Considering the close link between the intestine and the liver, the “detoxification” of gut-derived toxins, such as LPS and microbial products, is an important process played by the liver. Furthermore, nonalcoholic fatty liver disease is also associated with an increase in serum LPS levels, and the activation of the pro-inflammatory cascade plays a central role in the progression of the disease. Unfortunately, inflammation of the intestines triggers a downregulation of the detoxification mechanisms, such as CYP, Phase II and Phase III enzymes. This, in turn, creates a negative short circuit for the whole organism because the toxic substances which are not eliminated by the liver enter the general circulation by engaging the immune system, in particular macrophages, for their elimination, thus creating the basis for a chronic state of low-grade systemic inflammation. Among the substances which are useful, alpha lipoic acid (ALA) is important for the reduction of intestinal inflammatory phenomena and the activation of liver detoxification. ALA is useful in intestinal inflammation induced by trinitrobenzenesulfonic acid (TNBS) in rats through suppression of neutrophil accumulation. ALA is also useful to preserve the endogenous glutathione reservoir, through activation of an antioxidant response element (ARE) or the Nrf2 signaling pathway, fundamental for the activation of phases II and III of liver detoxification enzymes (MDRP, GpP, Oat2), and to inhibit reactive oxidant species[25].

Medicinal Mushrooms and Microbiota

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Mushrooms have long been used for medicinal purposes for over a thousand years for their health-promoting properties. Cumulative evidence obtained from animal models and human intervention studies strongly suggest their immunomodulatory, anti-allergic, anti-cholesterol, neuroprotective and anti-cancer properties[26]. Immune modulatory effect of β-glucans has been well described while studies on their action on microbiota have been increasing in the last decade.

Apart from exerting the health-related benefits mentioned above, mushrooms’ β-glucans and other molecules, such as polyphenols, trehalose and chitin, may also provide health promoting effects through their action as potential prebiotics. Published data have demonstrated that they act as prebiotics by stimulating the growth of a beneficial gut microbiota, conferring additional health benefits to the host. Highly branched insoluble non-digestible β-glucans contained in mushrooms are excellent prebiotics and are fermented by the microbiota[27].

Ganoderma lucidum has been reported to reduce obesity in mice by modulating the composition of gut microbiota. It also improves the gut barrier, attenuates endotoxemia, reduces inflammation and insulin-resistance, while improving dysbiosis and obesity-related metabolic disorders[28].

Lentinula edodes alters the spatial structure of gut microbiota in mice and acts as an antibiotic agent against pathogens[29].

Hericium erinaceus induces changes in the composition and activity of the gastrointestinal tract microbiota, confers nutritional and health benefits to the host and displays nootropic properties[30,31].

The mushrooms' effect on microbiota extends to an improvement of the gut-brain axis, which is recognized as being very important in maintaining homeostasis. This axis has been described as a bidirectional communication that can influence brain and gut health and, when disrupted, it may increase the risk of developing psychiatric, neurodevelopmental, age-related, and neurodegenerative disorders on one side, and gastrointestinal problems on the other side. This bidirectional communication takes place *via* various routes, including the immune system, neurotransmitter metabolism, the vagus nerve and the enteric nervous system, involving microbial metabolites, such as SCFA[32]. Previous studies carried out at the University of Pavia demonstrated the beneficial effects of AVD Micotherapy Hericium on the central nervous system, with memory and mood improvement. *Hericium erinaceus* may exert its effects through both the central and the enteric nervous systems and the gut microbiota, thus improving the gut-brain axis[33]. Moreover, research on low-molecular weight compounds of *Hericium erinaceus*, such as hericenones and erinacines, demonstrated their ability to cross the blood-brain barrier and to induce mRNA expression for nerve growth factor biosynthesis[34].

Similar nootropic activities have been described for *Ganoderma lucidum*, which enhances memory and learning in mice[35], makes favorable changes in cerebral blood flow, and improves the ratios of neurometabolites[36].

The gut microbiota plays a significant role in human health and disease. So far, the research on the regulation of microbiota by various mushrooms is steadily growing and the results are promising.

The Importance of Gut Microbiota in Cancer Patients

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Gut microbiota, a group of 10^{14} bacteria, eukaryotes and viruses living in gastrointestinal tract (GIT), is crucial for many physiological processes and, in particular, plays an important role in inflammatory and immune reactions. The gut bacteria can modulate both innate and adaptive immunity in the GIT. These microorganisms are helpful in physiologic activities, such as digestion, metabolism, epithelial homeostasis and development of gut-associated lymphoid tissues; moreover, they can synthesise vitamins (B and K), while their antigens and their metabolic products can stimulate the production of cytokines against potential pathogens. The distribution of bacteria varies along the GIT, ranging from 101 colony-forming units (CFU) per gram of contents in the esophagus and stomach to 1012 CFU per gram of contents in the colon, and distal gut disruption in the composition of these microbial communities can dysregulate host cellular processes and promote the development of various diseases, including cancer. Moreover, evidence20 has also shown that various environmental and host-related factors, such as maternal microbiota composition, birth patterns, breastfeeding, drug exposure, diet and genetic factors can alter the microbial ecosystem to such an extent as to have an impact on its resistance and resilience, which in turn has consequences on the immune and anti-inflammatory responses that are responsible for autoimmune, neurodegenerative, and IBD. Several observations support the idea that human gut microbiota dysbiosis can trigger inflammatory signaling pathways that affect the intestinal and extra-intestinal immune function and contribute to carcinogenesis and cancer progression. For example, some bacteria such as *Fusobacterium nucleatum* and *Ruminococcus/Faecalibacterium* play a crucial role in the carcinogenesis and the inflammatory process of colorectal cancer (CRC), and in the response to immunotherapy treatment, respectively. Moreover, *F. nucleatum* promotes CRC proliferation by binding its adhesin FadA to E-cadherin on CRC cell surfaces[37]; a recent preliminary study[37] also highlight the role of *F. nucleatum* in the CRC metastatic process. The potential manipulation of gut microbiota is of interest in the prevention and treatment of human gastrointestinal cancers. In this context, the role employed by probiotics in conferring gastrointestinal health and potential prevention of gastrointestinal cancers includes the production of SCFA, production of antimicrobial products, modulation of microbiota, reduction of inflammation, alteration of tumor gene expressions, modification of the differentiation process in cancer cells, inhibition of the pro-carcinogens, and activation of the host's immune system[38]. Overall, the results of clinical trials showed that probiotics can manipulate the composition of gut microbiota, improve intestinal barrier integrity, inhibit pathogen growth, and reduce metabolism of pro-carcinogenic substances[38]. Osterlund et al[39] demonstrated that the use of probiotics (*L. rhamnosus* GG for 24 weeks), in CRC patients treated with radiation-chemotherapy, was able to reduce diarrhoea, abdominal pain, and hospital care and radiation therapy-related toxicity[39]. Further clinical trials are needed to understand the role of microbiota in cancer disease and its potential role as a prognostic factor in all stages of the disease and as an immunomodulator and/or chemo-radio sensitizer during oncological treatment.

The Importance of Gut Microbiota in Amateur and Elite Athletes

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The composition of the gut microbiota, a highly dynamic and individualized ecosystem, can be influenced by a number of different factors, including physical exercise. Although physical activity alone is able to alter the human gut microbiota in terms of composition and function, there are a series of variables to be considered, such as the athlete's past history, the level and intensity of the activity practiced, and dietary intake in terms of both calories and micro- and macronutrients[40]. Physical exercise increases the bacterial species that produce SCFA, especially butyrate, which causes changes in the pH of the gut lumen, stimulating the growth of certain bacterial strains to the detriment of others. Butyrate also induces mucin synthesis, which improves the integrity of the intestinal membrane and increases tight junction assembly and reduces the conversion of primary bile salts into secondary ones. Primary bile salts have antimicrobial activity; more specifically, colic acid stimulates the growth of Firmicutes to the detriment of Bacteroidetes, consequently altering the Firmicutes/Bacteroidetes ratio[41]. Differences in the composition of microbiota can be seen not only between sedentary and active individuals, but also between individuals who practice physical activities at different levels or who practice different sports. The microbiota of active individuals shows a greater abundance of "health promoting" bacterial species, greater biodiversity and the presence of *Akkermansia muciniphila*, a bacterial marker of a healthy fitness profile[42,43]. In one recent study, stool samples of athletes participating in the Boston marathon (collected one week before and after the marathon), showed a significant increase in *Veillonella atypica* (a Gram-negative diplococcus of the phylum Firmicutes). Veillonella favors the conversion of lactate, induced by exercise, into propionate, a short-chain fatty acid. Furthermore, these athletes also showed a relative abundance not only of *Veillonella*, but also of Bacteroidetes, *Prevotella, Methanobevibacter* and *Akkermansia*[44]. The microbiota of athletes also presents an increased capacity to obtain energy from diet, with an increased capacity to metabolize carbohydrates and amino acids and to synthetize nucleotides and cell structures. This guarantees an increased functional capacity for tissue repair and an increase in the metabolic flexibility required to obtain energy from diet, by drawing on the metabolism of both carbohydrates and fats. However, the exercise-induced changes in microbiota composition are temporary and require constant simulation[45]. Consequently, diet and supplementation are important to maintain a healthy microbiota in athletes. As a matter of fact, many supplements used in sports nutrition affect the composition of the gut microbiota, including polyphenols, glutamine, turmeric, omega 3 and vitamin D. Orally administered polyphenols interact with the microbiota on different levels. Flavonoids can influence and remodel the composition of microbiota by exerting prebiotic effects, as demonstrated by *in vitro* and *in vivo* experiments. Preclinical and clinical studies have shown that polyphenols from supplements and foods stimulate the growth of beneficial bacteria, such as lactobacilli and bifidobacteria. Other species whose growth is favored by polyphenols include *Akkermansia*, *Faecalibacterium prausnitzii* and *Roseburia*, which also characterize the microbiota of the lean phenotype[46].

Literature evidence regarding the action of omega 3 on microbiota suggest a decrease in the Firmicutes/Bacteroidetes ratio, and levels of Coprococcus and Faecalibacterium, with an increase in Bifidobacterium, Lachnospira, Roseburia, Lactobacillus and other genera of butyrate-producing bacteria. More specifically, omega-3 PUFA levels are associated with Lachnospiraceae, a family of bacteria that produce SCFA. Curcumin and its derivatives also exert direct regulatory effects on the gut microbiota, significantly improving the ratio between beneficial microbiota and pathogenic agents, thereby significantly increasing the abundance of bifidobacteria, lactobacilli and butyrate-producing bacteria. *In vivo* studies[47] have also shown that curcumin modulates the Firmicutes/Bacteriodetes ratio, thereby modifying the microbial ecology of the gut and simultaneously exerting an anti-inflammatory action. Curcumin also reduces the proliferation of enterococci, coriobacterales and enterobacteria and promotes the integrity of the intestinal barrier, consequently exerting an immunomodulatory and anti-inflammatory action. As far as vitamin D is concerned, it should be pointed out that in addition to genetic factors, epigenetic factors, such as microbiota composition, can also determine the individual response to supplementation. More specifically, responders to vitamin D show an increase in Bacteroidetes, Actinobacteria, Proteobacteria and Leptosphaeria, and a decrease in Firmicutes. Non-responders, on the other hand, show an increase in Proteobacteria, *Bacteroides acidifaciens* depletion and a high Firmicutes/Bacteroidetes ratio[48].

The SFCA absorbed in the gut lumen modulate the host's metabolism, acting on various target organs, the largest of which is muscle, thereby characterizing the gut-muscle axis. By binding with the GPR41 and GPR43 receptors of muscle cells, SFCA induce the phosphorylation of AMPK, consequently promoting a catabolic pathway. As a matter of fact, one of the downstream targets of phosphorylated AMPK is PGC1α, which regulates mitochondrial biogenesis and promotes the metabolism and oxidation of carbohydrates and fats[49,50].

CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, we believe that scientific knowledge on human gut-microbiota represents a new challenge in all areas of medicine and a multidisciplinary and integrative approach is the right interpretation to improve the clinical results and our patients' quality of life. In the next future, our wish is to propose and organize prospective studies, within the IMRG, with the aim to improve the knowledge of various categories of patients, treated within a program of multidisciplinary and integrative approach.

Conflict of Interest

Dr Pier Paolo Zanello, Dr Stefania Cazzavillan, and Daniele Santagà are scientific consultants for AVD Reform.

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Scientific Manager of the Event

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