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Review

CORRELATION BETWEEN IBD, INTESTINAL DYSBIOSIS, DIET AND MOOD TONE DISEASE: ANALYSIS OF LITERATURE

Francesco Carini [1,2], Noemi Irma Bressan*[1,2], Irene La Palerma*[2], Dario Saguto[6], Guido Zanghì[7], Margherita Mazzola[1], Claudia Galletta[3], Giulia Tomasello[5], Giorgio Maida [1,4*], Marta Zanghì[8], Riccardo Gaglio[9], Giovanni Tomasello* [1]*

1."BIND" Department, School of Medicine, Palermo University, Italy.
2. Student School of Medicine, Palermo, Italy
3. Student in Food Science and Human Nutrition, Palermo University, Italy.
4. Student of Biotechnology, "STEBICEF" Department, University of Palermo, Italy.
5. Clinical Psychology, Palermo.
6. MD, "BIND" Department, School of Medicine, Palermo University, Italy.
7. Department of General Surgery and Medical - Surgical Specialities, Policlinico Vittorio Emanuele Hospital, University of Catania, Italy
8. Research Center on Motor Activities (CRAM), University of Catania, Italy
9. Specialist in Psychology and Psycoterapy

**These authors equally contributed to the work.*

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ABSTRACT

This essay's main goal of the present review is to highlight the connections between intestinal dysbiosis and the ensuing activation of the mucosal lymphatic system. One of the study's goals is to investigate the impact on mood caused by a serotonergic deficit driven by mucosal inflammation. It assesses the relationship between food consumption and the onset of psychological and mental illnesses as a secondary end aim. Patients with inflammatory bowel diseases and psychological and psychiatric mood disorders appear to benefit therapeutically from the sort of diet they consume.

1. Introduction

Numerous microorganisms coexist in harmony in human colon to form the intestinal microbiota, which is divided into four key groups: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Endogenous and exogenous factors including diet, medications, psycho-physical stress, and lifestyle have a long-lasting impact on this microbiome. A condition known as dysbiosis can affect the intestinal flora in specific circumstances.

Dysbiosis, which is defined as an imbalance between the symbiotic species, not only causes Inflammatory Bowel Disease (IBD) but it is also the onset of Irritable Bowel Syndrome (IBS).

Data from the literature highlight significant links between microbial imbalance and the development of chronic inflammatory bowel disorders.

This paper is focused on the correlation between dysbiosis, which activates the mucosal lymphatic system (Gut Associated Lymphoid tissue, or GALT), mucosal inflammation, and the ensuing mental problems. [(1)]

The gut-brain axis connects the peripheral and central neural systems to the intestine creating a bidirectional communication.

* *Corresponding author*: Giorgio Maida, *giorgiomaida25@gmail.com*
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This relation forms the cornerstone of a two-way cause-and-effect interaction that amply justifies the existence and growing significance of this union as the root of both intra- and extra-intestinal diseases. [1,2]

2. Material and methods

Intestinal dysbiosis, GALT activation, minor and major depression were used as search terms in PubMed to retrieve data from the scientific literature. Scientific articles and the book Diseases of the Digestive System Ed. Unigastro 2019 have both been evaluated.
Microsoft Word was the program utilized for the drafting.
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3. Correlation between dysbiosis and IBS - IBD

Inflammatory bowel disease (IBD) that has a recurrent course, intestinal symptoms, and potential extra-intestinal signs is known as chronic inflammatory bowel diseases (CIBD).
Although their pathophysiology is unclear, there is a connection between their manifestation and changes in the intestinal flora. [1]
In the table it is possible to take note of which bacterial species are able to increase or reduce intestinal inflammation (see Tab 1).
Dysbiosis has been shown to change the intestinal wall, making it thinner and increasing permeability as a result of altered tight junctions.
Dysbiosis contributes to the intestinal wall inflammation through a number of different pathways that influences how the GALT (Gut Associated Lymphoid Tissue) reacts since it is characterized by an increase in pro-inflammatory bacteria and a decrease in bacteria with anti-inflammatory properties.
The decrease of one of the phyla most prevalent at the gastrointestinal level (Bacteroidetes), as well as the reduction of Eubacterium and Faecalibacterium (Firmicutes), and the increase of Proteobacteria and Bifidobacteria, were specifically found in Crohn's disease (CD).
Contrarily, people with ulcerative colitis have higher levels of Proteobacteria Hamophilus than do those who are in remission, who have higher levels of Faecalibacterium and Lachnospira.
The presence of F. prausnitzii was found to be lower in patients with CD and rectal UC (ulcerative colitis) compared to individuals in remission, which raises the idea of employing these bacteria as a biomarker since its lower presence is associated with a higher risk of recurrence or severe MC activity (Gut Microbiota Is a Potential Biomarker in Inflammatory Bowel Disease).
Thus, probiotics are used to maintain the gut environment's equilibrium. Common probiotics-based therapy employs Lactobacillus and Bifidobacteria.
GALT is crucial for the detection of self antigens, local microbial flora, dietary antigens, and potentially dangerous antigens under normal circumstances. In the latter scenario, the antigen presentation by APC cells (Antigen-Presenting Cells) to the lymphocytes is crucial in defining the immune response's activation.
However, the antigens that may be in charge of initiating this process in IBD have not yet been discovered.
Although, it has been shown that T cells and macrophages can activate the cell-mediated immune response. This is why probiotics are used in order to keep the intestinal environment in balance.
Aggregates of T-lymphocytes and macrophages are found in biopsy samples from individuals with Crohn's disease. This pathology is characterized by the activation of T-helper 1 lymphocytes, responsible for the release of pro-inflammatory cytokines, such as: TNFα, IFNγ, IL-12, 1L-18 and IL-21 with the consequent maintenance of inflammation. This process is not limited only to the digestive tract, but involves the entire body, as demonstrated by the increase in blood inflammation indices: ESR (erythrocyte sedimentation rate) and CRP (C-reactive proteins).
Chronic systemic inflammation is at the basis of various diseases, including pancreatitis, thyroiditis, autoimmune diseases and mood disorders.

	REDUCTION	INCREASE
Bacteria	• *Bifidobacterium s.* • *Clostridium* • *Faecalibacterium prausnitzii* • *Roseburia s.* • *Suterella s.* • *Bacteroides s.*	• *Proteobacteria* • *Fusobacterium s.* • *Ruminococcus gnavus* • *Pasteurellaceae s.* • *Veillonellaceae s.*
Virus		• *Caudovirales*
Fungus	• *Saccharomyces cerevisiae*	• *Clavispora lusitaniae* • *Candida albicans* • *Candida tropicalis* • *Kluyverpmyces marxianus* • *Cyberlindnera jadini*
Archaea	• *Methanobrevibacter smithii*	• *Methanosphaerastastmanae*

Table 1. Most microbiota changes, which involve microorganisms like bacteria, interact with a rise in inflammation, Archaea, viruses, and fungus.

4. Correlation between diet, serotonin levels and mood turbe

This latter element should be clarified because phlogosis mediators are known to reduce serotonin levels.
Serotonin, also known as "the feel-good hormone" or 5-hydroxytryptamine or 5-HT, is a neurotransmitter that is produced in the brain and other tissues from the amino acid tryptophan. (90% of serotonin synthesis occurs at the level of enterochromaffin cells, and the remaining 10% takes place in the serotonergic neurons of the enteric nervous system.
The two subsequent steps of hydroxylation and decarboxylation, which are dependent on vitamin B6, turn tryptophan into serotonin. The daily intake of 1.3 mg of vitamin B6 should be met through the diet.
The estimated need for tryptophan is equal to 3.5 mg / kg per day. Food rich in tryptophan are dried fruit (especially cashews, walnuts, peanuts and almonds), seeds (sesame, pumpkin, sunflower), soy, cheese, fish, oats, beans, lentils, eggs and meats.
The gut microbiota plays a key role in the bioavailability of amino acids, including tryptophan. Dietary modifications can alter the microbial balance and consequently the synthesis of serotonin. A diet in which probiotics such as Lactobacillus and Bifidobacterium are present will bring numerous benefits to the metabolism of tryptophan, acting directly on its conversion into serotonin. [4]

Furthermore, by inserting prebiotics, such as FOS and resistant starch, there is an increase in the production of short-chain fatty acids (SCFA - acetate, propionate and butyrate) which promote the transcription of the gene (TPH1), involved in the catalysis of serotonin's first synthesis reaction, and the production of the latter by enterochromaffin cells. In addition, SCFAs stimulate intestinal motility, which is essential for maintaining serotonin homeostasis. [5)]

Serotonin is involved in numerous and important biological functions, many of which are still to be clarified.

Same as all chemical mediators, it acts by interacting with specific receptors, carrying out a different effect based on the body region considered. As a precursor of melatonin, it regulates circadian rhythms, synchronizing the sleep-wake cycle with daily endocrine fluctuations.

Other benefits include the regulation of appetite and eating habits, which leads to an earlier onset of fullness, a reduced intake of carbs in favor of proteins, and an overall decrease in the amount of food consumed. Unsurprisingly, many individuals who complain about a decline in mood experience a strong craving for so-called 'comfort foods' such as chocolate and sweets, high in simple carbs, which stimulate 'feel-good' reward pathways. Chocolate also contains theobromine, which has psychoactive effects. Following a meal, tryptophan levels rise, making it easier for it to enter the brain and enhance the synthesis of serotonin, which in turn causes a classic negative feedback cycle to reduce the urge for carbohydrates. Serotonin levels also rise during physical exertion, which partly explains the antidepressant effects of motor activity.

When serotonin levels are excessive or deficient, it can lead to diarrhea and when present in sufficient amounts, it can produce constipation. Serotonin modulates intestinal motility and secretions. Because of this unique action, which is sensitive to the interaction between the "enteric nervous system" and the central nervous system, intestinal motility is frequently affected by significant psychophysical stresses. [5)]

Low levels of serotonin seem to be associated with hypersexuality and aggressive antisocial behaviour. The serotonin system is also involved in the regulation of sexual behaviour and social connections. It is no accident that some substances, like ecstasy, that boost serotonin production and/or the activity of its receptors cause euphoria, an increase in sociability, and a boost to one's self-esteem. Serotonin inhibits hunger, pain sensitivity, and body temperature in addition to sexual behaviour.

A portion of serotonin interacts with postsynaptic receptors at the CNS level after it is released from the axon terminal, while the excess is either broken down by MAO (monoamine oxidase) or reabsorbed by the presynaptic terminal, where it is stored in specific vesicles. Since MAO-inhibitor medications increase the concentration of serotonin and other cerebral monoamines in the CNS, they are useful in the treatment of depression, even if their usage is currently being curtailed due to significant side effects. Serotonin deficiency can therefore result in states of depression, as well as anxiety and anger. At the level of the central nervous system, deficient serotonin levels are actually the source of abnormal mood swings. Many antidepressants function by preventing serotonin from being reabsorbed, which strengthens the signal of the neurotransmitter, which is especially weak in depressed individuals. An excess of serotonin causes nausea and vomiting, and it is no coincidence that this is one of the main side effects of various antidepressant drugs, nausea arises in the first week of therapy and then regresses.

Vagal system and gut-brain axis

Receptor	*FFAR2 (GPR*43)*	*FFAR3 (GPR41)*	*GPR*109A*
Name	Free fatty acid receptor (GPCR*43)	Fatty acid receptor 3 (GPCR41)	G Protein-Coupled Receptor (GPR*109A)
Localization	• colonic epithelium, • enteroendocrine cells, • mast cells, neutrophils, • macrophages, • T, regulatory T cells, • B Lymphocytes, • polymorphonuclear cells, • eosinophils, • adipocytes, • epithelium of the small intestine, • leukocytes (eosinophils, basophils, neutrophils, monocytes and dendritic cells), • skeletal muscle cells, heart and spleen	• colonic epithelium, • enteroendocrine cells, • epithelium of the small intestine, • mast cells, • spleen, • pancreas, • bone marrow, • lymph nodes, • adipose tissue, • peripheral blood mononuclear cells	• Apical colic membrane and/or small intestine epithelium • macrophages • monocytes, neutrophiles • dendritic cells • adipocytes • islands of Langerhans and retinal pigment epithelium
Localization in Central and Peripheric Nervous System	ND	• sympathetic ganglia, vagal and dorsal roots • trigeminal ganglia	Ventrolateral medulla and PC12 cells
SCFA substrates	acetate and propionate	acetate, propionate and butyrate	butyrate

Receptor	*OR51E1 (GPR164)*	*OR51E2 (Olfr78)*	*GPR42*
Name	Recettore olfattivo 51E1 (GPCR 164)	Recettore olfattivo 51E2 (Recettore olfattivo 78)	G Protein-Coupled Receptor (GPR42)
Localization	• Cardia's mucosa • Fundic mucosa • Pyloric and duodenal mucosa • Jejunal mucosa • Iliac mucosa • Cecal, colic and rectal mucosa	• Juxtaglomerular apparatus of the kidney • Arterial smooth muscle cells • Cardiac and intestinal innervation • Blood vessels • Melanocytes	Colon
Localization in Central and Peripheric Nervous System	ND	• Autonomous nervous system ganglia • Sphenopalatine ganglion	Sympathetic abdominal ganglia
SCFA substrates	Butyrate	Propionate, acetate	Propionate

ND: not determined
GPCR: G protein-coupled receptor
SCFA: Short Chain Fatty Acids

Table 1. Lists the names and locations of the receptors, including the sensory ones (olfactory receptor), that are found in many organs.

It is now understood that our intestine, or "second brain" is profoundly influenced by our central nervous system and vice versa. In fact, more connections travel from the gastrointestinal tract to the CNS than those that do the opposite. Therefore, gastrointestinal disorders can alter how the brain functions. This discussion is made much more interesting when we realize that the intestines are responsible for producing 95% of the serotonin in our bodies.

The "Vagus Nerve Stimulation" (VNS), a new treatment for depression announced in 2005, involves a small silver device implantation in the subcutis, close to the collarbone, in order to perform a direct pacemaker function on the nerve.

Antidepressant medications, gastrointestinal serotonin levels, and the role that the vagus nerve stimulation plays in boosting the transit of serotonin from the intestine to the brain have all been linked in recent years. [(7)]

In particular, it was observed that after a vagotomy, antidepressants lost the ability to relieve depressive symptoms (in mouse models). [(8)]

The long-term positive effects of VNS in patients with persistent depression provide proof that the vagus nerve can transfer signals to the brain that result in a reduction in depressed behavior. Finding new medications, dietary supplements, or probiotics that have the potential to positively modulate its activity is a great way to open up the door to new treatment options for some psychological and psychiatric disorders. It turns out to be the primary neural link between the intestine and the brain.

To sum up, additional research will be required to pinpoint specific gut microbiome elements that may be crucial for mental health and psychological well-being via the gut-vagus-brain axis. [9,10]

5. Conclusions

In this paper, we discuss the international literature's scientific findings on relationship between intestinal dysbiosis and the lymphatic system of the mucosa. A serotonergic deficit caused by mucosal inflammation has a deleterious impact on mood. The type of food consumed by individuals with inflammatory bowel disease affects mood by enhancing or escalating their depressive symptoms. In the near future, more research will be required to clarify the issue.

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