Current Understanding of Gut Microbiota

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The Gut Microbiome

- The human intestine contains 10 to 100 trillion microbes, which is almost 10 times greater than the total number of human cells and contains 150 times more unique genes than the human genome.

- Some researchers regard the human microbiota as the second genome.

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The Gut Microbiome

- The normal gut ecosystem is beneficial in maintaining health, which can be classified into metabolic, protective, structural, and histological functions .
- It has known that gut microbiota participates in many pivotal biological functions in human, including:
  - Brain development,
  - Immune maturation,
  - Endocrine and stress response pathways,
  - Coincide with the psychopathological pathways of affective disorders

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The Gut Microbiome

- The predominant bacterial phyla in the human GI are:
  - Firmicutes,
  - Bacteroidetes,
  - Proteobacteria,
  - Actinobacteria,
  - Fusobacteria,
  - Cyanobacteria

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The Gut Microbiome and Epigenetics

- The gut microbiota can be influenced by various factors, such as:
  - Genetic basis
  - Environment
  - Mode of delivery
  - Diet
  - Antibiotics
  - Probiotics and Prebiotics

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Environment

- Bacteria present in the mother's vaginal tract and on her skin serve as the first bacteria to colonize the neonate gut.

- Later, microbes present in the colostrum form a part of the gut microbiome

- Locality, ethnicity and culture affecting the gut microbiome

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Diet

- Switching from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar diet shifted the community structure of the microbiome within a single day.

- Changed the representation of metabolic pathways in the microbiome, and altered microbiome gene expression

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Probiotics and Prebiotics

- Probiotics are foods or supplements that contain live microorganisms intended to maintain or improve the "good" bacteria (normal microflora) in the body.

- Prebiotics are foods (typically high-fiber foods) that act as food for human microflora.

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The Gut Microbiome and Health

- Dysbiosis in gut microbiota was found to be associated with many systemic disorders, such as:
  - Functional bowel disorders
  - Inflammatory bowel disease
  - Autoimmune diseases
  - Atherosclerosis
  - Metabolic disease
  - Neuropsychiatric disorders

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The Brain-Gut-Microbiota Axis

- Studies indicated that altered gut bacterial communities could substantially influence the central physiology.

- Gut microbiota modulates brain development and function and the brain in turn interacts with gut bacteria via neuroimmune, neuroendocrine pathways, and the nervous system.

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The Brain-Gut-Microbiota Axis

Through this bidirectional communication system:

- Signals from the brain can influence the physiological effects of the gut, including motility, secretion and immune function,

- Messages from the gut can influence the brain function with regard to reflex regulation and mood states

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The Brain-Gut-Microbiota Axis

- Chronic stress could affect the gut microbiota composition, which is associated with the activation of the HPA axis and an elevation in the pro-inflammatory status

- The intestinal mucosal barrier and blood–brain barrier are important gates for substance transfer

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The Brain-Gut-Microbiota Axis

- “leaky gut”
- The cortisol can increase the permeability of the intestinal tract and blood–brain barrier, thus facilitating the mutual communication between the gut microbiota and the central nervous system (CNS)

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Gut Immune System

- Gut immunological homeostasis is influenced by host–microbe interactions.

- Microbiota-driven pro-inflammatory state and low-grade inflammation in dysfunctional intestinal mucosal barrier was observed in stress-related psychiatric disorders such as depression

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The Neural Pathway

- The communication between the gut and brain, through the neural anatomical pathway, is based on a hierarchic four-level integrative organization, including:
- ENS
- Prevertebral ganglia,
- The autonomic nervous system
- The CNS

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The Neural Pathway

The enteric nervous system (ENS)

- A web of sensory neurons, motor neurons, and interneurons embedded in the wall of the gastrointestinal system, stretching from the lower third of the esophagus right through to the rectum.
- Is a large division of the peripheral nervous system (PNS) that can control gastrointestinal behaviour independently of central nervous system (CNS) input.

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The Neural Pathway

- It seems that the effects of gut microbiota on the brain function are dependent on vagal activation.

- Furthermore, activation of the VN inhibits cytokine production, manifesting as an anti-inflammatory response.

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The Neural Pathway

- Gut microbiota can secrete a series of neurotransmitters, such as:
  - **γ-aminobutyric acid (GABA)**
  - **Acetylcholine**
  - **Serotonin**
  - **Dopamine**
  - **Histamine**
  - **Noradrenalin**

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The Neural Pathway

- More than 90% of the neurotransmitter, serotonin, in the human body is produced in the gut, which can affect emotion regulation when transmitted to the CNS

- It is conceivable that neurotransmitters secreted by gut microbiota can influence the level of central neurotransmitters and then affect behavior and mood

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The Neural Pathway

- Furthermore, bacterial metabolites, such as SCFAs have physiological effects:
  - Regulation of food intake,
  - Glucose/insulin or lipid metabolism,
  - Anti-inflammatory and antitumorigenic functions,
  - Activate the sympathetic nervous system
- Butyrate can alter the activity of cells located in the blood–brain barrier and exert an antidepressant-like effect in animal models

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The Neural Pathway

- In depressed patients, decreased microbial diversity was found in most studies.

- According to different studies, a consistent increase in the abundance of Actinobacteria, Enterobacteriaceae and a decrease in Faecalibacterium was revealed.

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Gut Microbiota and Neuropsychiatric Disorders

- Gut microbiota plays an underlying role in several stress-associated neuropsychological conditions, including anxiety and depressive disorders.

- The CNS neurotransduction can be profoundly disturbed by the absence of a normal gut microbiota and that this aberrant neurochemical, but not behavioral, profile is resistant to restoration of a normal gut flora in later life.

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Gut Microbiota and Depressive Disorders

- There is no specific‘ dysbiosis’ signature found in depression.
- Currently, there are five probiotic RCTs using predominantly Lactobacillus and Bifidobacterium species to treat depression.
- A small Iranian RCT tested the impact of Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis and Lactobacillus acidophilus.

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Gut Microbiota and Schizophrenia

- Schizophrenia is mainly a heritable disorder; however, many researchers assume a possible etiological role of the gut microbiome through epigenetic modulation (i.e. diet and exposure to infectious agents).
- Three RCTs, did not find a significant difference in schizophrenia symptoms between probiotic and placebo groups postintervention when applying a per-protocol analysis and a fixed effects model.

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Gut Microbiota and Autism Spectrom Disorders

- Alternations in gut microbial composition have been observed in children with **ASD**, with an increase in the Firmicutes/Bacteroidetes ratio.
- Butyrate/lactate-producing bacteria were decreased.
- Patients with **schizophrenia** also showed dysbiosis of gut microbiota, with a higher Proteobacteria_abundance compared to the healthy controls
- Increased abundance of Lactobacillus in patients with **first-episode psychosis**

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Gut Microbiota and Epilepsy

- A study assessed the microbiota profile in 42 treatment-resistant epileptic patients vs. 49 treatment-responsive patients and found significant differences in the composition of gut microbiota.
- Patients with four seizures per year or fewer showed an increase of Bifidobacteria and Lactobacillus compared to those with more than four seizures per year.

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Gut Microbiota and Migraine Headache

- Increased level of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, resulting from the “leaky gut”, could affect nociceptive responses in the trigeminal pathway and play a role in migraine pain initiation.

- Probiotic administration significantly inhibited the antibiotic-produced migraine-like pain prolongation.

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Gut Microbiota and Parkinson's disease

- Motor symptoms related to Parkinson's disease are often preceded by dysregulation in GI functions, manifested as bloating, nausea, constipation, gastroparesis, or weight loss
- There are common factors in the pathophysiology of Crohn's and Parkinson's diseases, e.g., variants in the CARD15 and LRRK2 genes are involved in the pathogenesis of both diseases

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Gut Microbiota and Parkinson's disease

- GI tract may be responsible for the spread of Parkinson's disease, since inclusions of α-synuclein may at first appear in the ENS and only later they are transmitted to the CNS via the glossopharyngeal or vagal nerves.
- There is evidence coming from both preclinical and clinical studies that the "leaky gut" may cause α-synuclein aggregation

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The Impact of Psychotropic Medication on the Gut Microbiota

- Significantly decreased microbial diversity was revealed in AAP-treated females.
- Chemically different antipsychotics and antidepressants can exert inhibitory effects on the growth of gut-originated microbial strains, indicating that these non-antibiotics have antibiotic-like side effects (Maier et al., 2018).

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The Impact of Psychotropic Medication on the Gut Microbiota

- Most psychotropic medications target neurotransmitters and their receptors, including serotonin, dopamine and noradrenalin, which can also be produced by gut microbiota and can potentially have feedback on the bacteria.

- Furthermore, improvement of clinical symptoms, through psychotropic medications, may also influence the diversity and composition of gut microbiota.

- The gastrointestinal side effects of these drugs, such as constipation and diarrhea, may also affect the commensal bacteria.

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Modification (Psycho-biotics)

- The MGBA can be modified with:
  - Certain prebiotics (dietary modification/diets rich in non-digestible fibre),
  - Probiotics (living bacteria),
  - Synbiotics (combinations of pre- and probiotics),
  - Postbiotics (bacterial fermentation products such as short chain fatty acids (SCFAs)
  - Antibiotics
  - Faecal microbiota transplantation (FMT)

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