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A Review of Relation Between Agnibala, Gut Microbe and Depressive Disorders

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ABSTRACT
The purpose of this review is to find out the relation between gut microbiota and depressive disorders. In many studies, it is proven that the mortal gastrointestinal (GI) tract harbors a complex and dynamic population of microorganisms, the gut microbiota, which exerts a prounced influence on the host during homeostasis and complaint. Multiple factors contribute to the establishment of the mortal gut microbiota during immaturity. One of the primary factors influencing the gut microbiota throughout life is thought to be diet. In order to protect the body from infections and preserve metabolic equilibrium, intestinal bacteria are essential. Dysbiosis, or altered gut bacterial makeup, has been linked to the etiology of several diseases and inherited illnesses. A deeper comprehension of inter-individual variety, the complexity of bacterial populations along and across the GI tract, functional redundancy, and the necessity of differentiating cause from effect in symbiosis-affected nations are all necessary for interpreting these data. In order to support the need for mechanistic studies focused on host-microbe relations, this review highlights our present understanding of the evolution and composition of the mortal GI micro biota and its impact on gut integrity and host health.
KEYWORD- Depressive Disorders, Gut Microbe, Agnibala, Digestion, Gastroenterology, , Neurotransmitter, Mental Health, Diet.

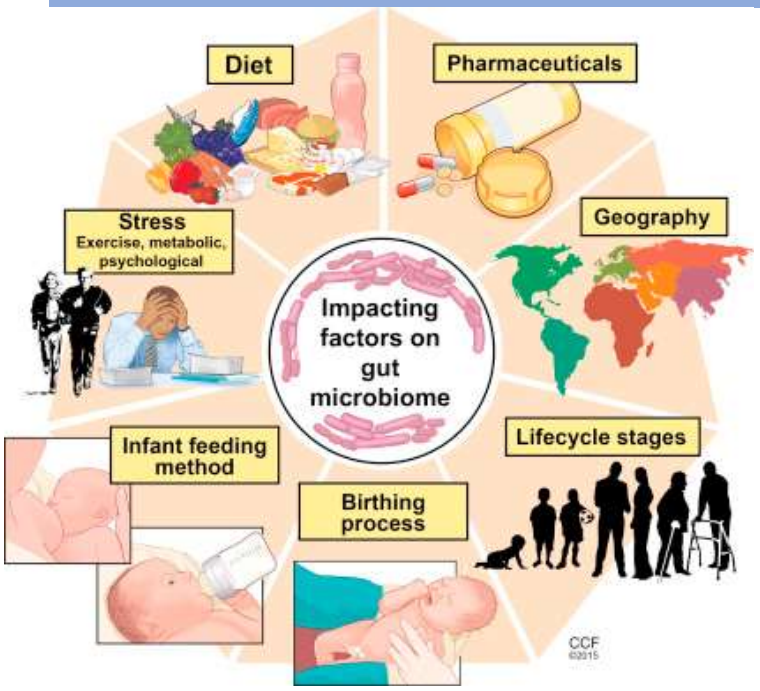
INTRODUCTION:-

Gut Microbes in are most important to the human body (**Ruairi Robertson)**. The composition of one's gut micro-biota is individually specific and is highly influenced by genetics, growth and development, and location. With an estimated 1018 micro-organisms, mostly made up of anaerobic bacteria, the gut micro biome is responsible for multiple functions in bowel movement, digestion of food, and absorption of nutrients **(Therese Limbana, Farah Khan, and NohaEskander)**.

The mortal gastrointestinal (GI) tract represents one of the largest interfaces (250–400 m^2) between the host, environmental factors and antigens in the mortal body. In an average life time, around 60 tonnes of food pass through the mortal GI tract, along with a cornucopia of microorganisms from the terrain which put huge trouble on gut integrity. The collection of bacteria, archaea and eukarya colonising the GI tract is nominated the 'gut microbiota' and has co-evolved with the host over thousands of years to form an intricate and mutually salutary relationship. The number of microorganisms inhabiting the GI tract has been estimated to exceed 10^{14}, which encompasses ~10 times salutary bacterial cells than the number of mortal cells and over 100 times the quantum of genomic content (microbiome) as the mortal genome. Still, a lately revised estimate has suggested that the rate of human bacterial cells is actually near to 11. As a result of the vast number of bacterial cells in the body, the host and the microorganisms inhabiting it are frequently appertained to as a 'super organism' (**Gill S.R., Pop M., De Boy R.T., Eckburg P.B., Turnbaugh P.J., Samuel B.S. et al**.)

The gut microbiome, as explained by molecular biologist Joshua Lederberg, is the totality of microorganisms, bacteria, viruses, protozoa, and fungi, and their communal genetic material existing in the gastrointestinal tract (GIT). The gut microbiota is encompassed of all the bacteria, commensal, and pathogenic, residing in the GIT. In the past era the gut microbiota has been explored for potential gut microbe–host connections comprising effects on metabolism, immune, and neuroendocrine reactions. The gut microbiota plays an important role in nutrient and organic absorption, synthesis of enzymes, vitamins and amino acids, and production of short-chain fatty acids (SCFAs). The fermentation by products acetate, propionate, and butyrate are vital for gut health and provide energy for epithelial cells, enhance epithelial barrier integrity, and provide immunomodulation and protection against pathogens**(Gail A.M. Cresci , Kristin Izzo).**

The mortal gut microbiota is divided into numerous groups called phyla. The gut microbiota is embraced mainly of 4 main phyla which include Firmicutes, Bacteriodetes, Actinobacteria, and Proteobacteria (Belizario and Napolitano, 2015). While bacteria colonizes the mortal body, including oral depression, placenta, vagina, skin, and GIT, the maturity of bacteria live within the GIT, with the maturity of generally anaerobic bacteria housed in the colon. To gain perspective of the magnitude of bacterial presence and implicit goods on the host, the mortal body expresses 20,000 eukaryotic genes while the gut microbiome expresses3.3 million prokaryotic genes (NIH, 2012) **(https://www.sciencedirect.com/topics/medicine-and-dentistry/gut-microbiome).**



CONCEPTS IN MENTAL HEALTH

Mental health is a state of internal well- being that enables people to manage with the stresses of life, realize their capacities, learn well and work well, and contribute to their community. It's a primary component of health and well- being that underpins our individual and combined capacities to make opinions, make connections and shape the world we live in. Mental health is an introductory mortal right. And it's essential to particular, community and socio- profitable development.

Mental health is further than the absence of internal diseases. It exists on a complex continuum, which is educated else from one person to the coming, with varying degrees of difficulty and torture and potentially veritably different social and clinical issues. Mental health conditions include internal diseases and psychosocial disabilities as well as other internal countries associated with significant torture, impairment in performing, or threat of tone- detriment. People with internal health conditions are more likely to witness lower situations of internal well- being, but this isn't always or inescapably the case**.** **(https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response)**

According to the **World Health Organization (WHO):**

"*Mental health is a condition of mental happiness that enables individuals to manage with the stresses of life, understand their abilities, learn well and work well, and add to their community*."

The WHO states that mental wellbeing is "more than just the non-appearance of mental disorders or disabilities." Peak mental wellbeing is not only about managing active conditions but also observing after on-going wellness and happiness. It also highlights that preserving and restoring mental wellbeing is crucial individually and at a community and society

level. In the United States, the National Alliance on Mental Illness evaluations that almost 1 in 5 adults experience mental health problems each year.

In 2020, a predictable 14.2 million adults in the U.S., or about 5.6%, had a serious mental condition, according to the National Institute of Mental Health (NIMH). (**https://www.medicalnewstoday.com/articles/154543#definition**)

No somatic test or scan constantly indicates whether a person has developed a mental illness. However, individuals should look out for the following as possible signs of a mental health syndrome:

- withdrawing from friends, household, and workfellows
- avoiding actions they would normally enjoy
- sleeping too much or too little
- appetite too much or too little
- feeling worried
- having consistently low drive
- using mood-altering materials, including alcohol and nicotine, more frequently
- displaying negative reactions
- being confused
- being not capable to complete daily tasks, such as getting to work or cooking a meal
- having persistent thoughts or reminiscences that reappear regularly
- thinking of causing bodily harm to themselves or others
- hearing sounds
- Experiencing misbeliefs.

Diagnosing a psychological health complaint requires a multi-step process. A doctor may begin by looking at a person's medical history and performing a thorough somatic exam to rule out bodily circumstances or issues that may be causing the indications. Most mental health experts use the American Psychiatric Association's (APA) **Diagnostic and Statistical Manual of Mental Disorders (DSM-5)** to make a diagnosis. This manual contains descriptions and specific standards to qualify for a judgment.

RISK FACTORS FOR MENTAL HEALTH CONDITIONS

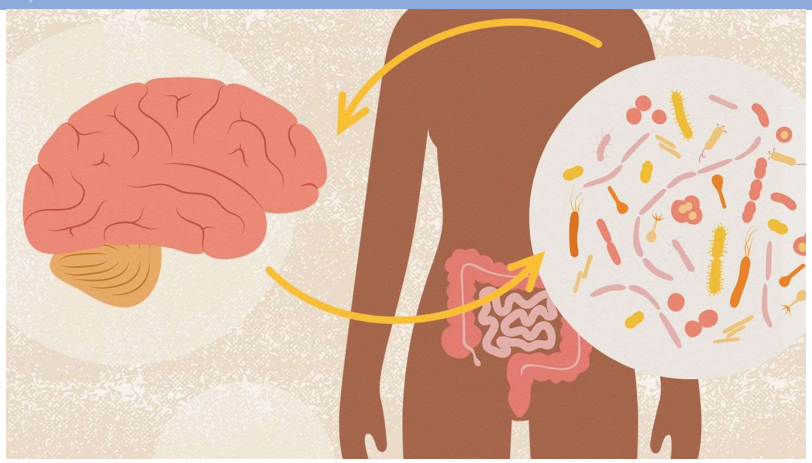
Everybody is at some danger of developing a mental health complaint, regardless of age, sex, income, or ethnicity. In the U.S. and much of the advanced ecosphere, mental illnesses are one of the leading causes of incapacity.

Communal and economic situations, adverse childhood experiences, biological factors, and underlying medical conditions can all shape a person's psychological wellbeing. Many individuals with a mental wellbeing disorder have more than one condition at a time.

It is important to note that good psychological wellbeing depends on a delicate balance of factors and that several essentials may contribute to developing these complaints (**Adam Felman and Rachel Ann Tee-Melegrito).**

GUT AND BRAIN CONNECTION

With the brain and the gut functioning in a bi-directional way, they could affect each other's functions and significantly impact stress, anxiety, depression, and perception**(*Limbana T, Khan F, Eskander N (August 23, 2020)***



Depressive disorders are the main communal health concern. In 2017, the World Health Organization (WHO) declared that depressive disorders became the leading cause of disability worldwide (W.H.O., 2017). Depression is a serious mental illness caused by various factors. It is described as low expressive disposition, loss of self-reliance, and apathy. Depression is suggested to outcome from complex interactions of person's genetics and their environment (nature and nurture).

Given how closely the gut and brain relate, it becomes easier to understand why person might feel nauseated before giving a performance, or feel intestinal pain during times of strain. That doesn't mean, still, that functional gastric circumstances are imagined or "all in head." Psychology syndicates with physical aspects to cause discomfort or pain and other bowel indicators. Psychosocial factors affect the actual physiology of the gut, as well as symptoms. In other words, stress (or depression or other psychological factors) can disturb movement and contractions of the GI tract.

In addition, many people with practical GI disorders perceive pain more acutely than other persons do because their brains are more reactive to pain signals from the GI tract. Stress can make the existing discomfort seem even worse.

Multiple studies have found that psychologically based tactics lead to greater development in digestive symptoms compared with only conventional medical dealing(**https://www.health.harvard.edu/diseases-and-conditions/the-gut-brain-connection).**

MULTIPLE FACTORS LEADS TO DEPRESSION

Major depressive disorder (MDD) tops the spot in causative to the worldwide disease burden, as claimed by the World Health Organization (WHO). Based on the WHO reports, there are approximately 350 million people affected by depression ***(Limbana T, Khan F, Eskander N).*** Research findings showed that healthy gut micro-flora transmits brain signals through the pathways involved in neurogenesis, neural transmission, microglial activation, and behavioral control under stable or stressful conditions. This process led several studies to recognize the importance of micro-biomes in managing mental health issues ***(Sherwin E, Rea K, Dinan TG, Cryan JF).***

In depression, there is also deregulation of the neuroendocrine and neuro-immune pathways(***Kelly JR, Keane VO, Cryan JF, Clarke G, Dinan TG).*** Pathophysiology of Depressive Disorder Dopamine System The monoamine hypothesis might be the best-known etiological hypothesis for MDD(***Moulton CD, Pavlidis P, Norton C, Norton S, Pariante C, Hayee B, Powell N).***

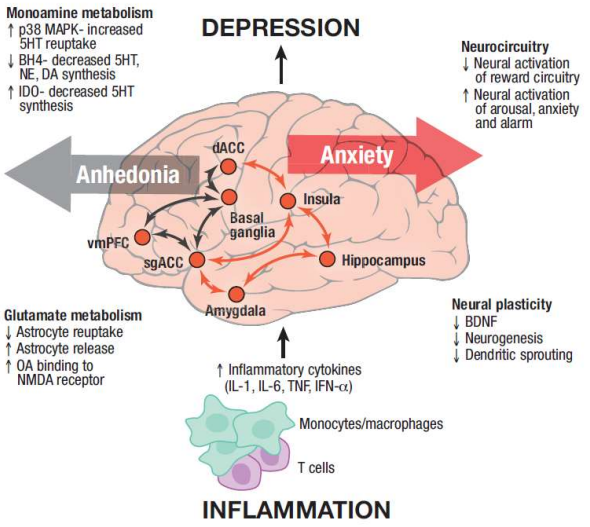


Figure Impact of inflammation on the brain and behavior
5HT, serotonin; BDNF, brain derived neurotrophic factor; BH4, tetrahydrobiopterin; DA, dopamine; dACC, dorsal anterior cingulate cortex; IDO, indoleamine 2,3 dioxygenase; IFN-interferon; IL, interleukin; MAPK, mitogen activated protein kinase; NE, norepinephrine; NMDA, N-methyl-D-aspartate; QA, quinolinic acid; sgACC, subgenual anterior cingulate cortex; TNF, tumor necrosis factor.

Any classes of antidepressants exert their effects through rising monoamine neurotransmitters (serotonin, noradrenaline, and/ or dopamine) in the synaptic cleft. Given the results from in vitro studies that first-line antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors inhibit the reuptake of serotonin and noradrenaline, one might doubtful that these 2 neurotransmitters play more vital roles than dopamine***(Chiba S, Numakawa T, Ninomiya M, Yoon HS, Kunugi H. Cabergoline)***.However, the recent confirmation from the cerebrospinal fluid (CSF) suggests its opposite direction. Among monoamine metabolites, homovanillic acid (HVA, a primary dopamine metabolite) but not 5-hydroxyindoleacetic acid (a primary serotonin metabolite), or 3-methoxy-4-hydroxyphenylglycol (MHPG: a primary noradrenaline metabolite), was shown to be significantly reduced in the CSF of MDD patients. In line with this, in vivo animal studies using micro-dialysis have demonstrated that many of the SSRIs increase extracellular dopamine as well as serotonin in the prefrontal cortex, despite the fact that SSRIs do not inhibit the reuptake of dopamine in vitro. The increase in dopamine could be central to the antidepressant effects. Indeed, at least a portion of MDD is responsive to dopamine agonists, and such drugs increase BDNF levels in the cerebral cortex and hippocampus in animal studies(***Adachi N, Yoshimura A, Chiba S, Ogawa S, Kunugi H. Rotigotine)***.

RELATION BETWEEN STRESS AND DEPRESSION:

Altered Stress Response MDD is often induced by chronic stress; therefore, abnormal stress response in the HPA axis is one of the most extensively studied biological markers for depression**(Kunugi H.)**. Initially, typical MDD subtypes such as melancholic and psychotic forms were found to have improved HPA activity due to inadequate negative feedback of the HPA axis detected by hormonal challenge tests such as the dexamethasone (DEX) suppression test and DEX/ corticotrophin-releasing hormone (CRH) test**(Kunugi H.).**

In line with this, it has been also reported, enhanced cortisol responses in the DEX/ CRH test in Japanese MDD inpatients before treatment and its recovery after treatment**(Linda Carpenter, Nicole Ross Audrey Tyrka, George R Aderson)**. However, subsequent studies have revealed that depressed patients as a whole showed similar, or even attenuated, cortisol responses as compared to healthy controls in the DEX/CRH test. In these studies, patients had clinical characteristics such as outpatients, chronic cases, depressive patients with psychiatric comorbidity, or long-term sick-leave patients**(Linda Carpenter, Nicole Ross Audrey Tyrka, George R Aderson)**. These inconsistent findings are related to the heterogeneity of the illness. Indeed, atypical depression and other stress-related conditions such as posttraumatic stress disorder, chronic fatigue syndrome, and fibromyalgia are associated with attenuated, rather than

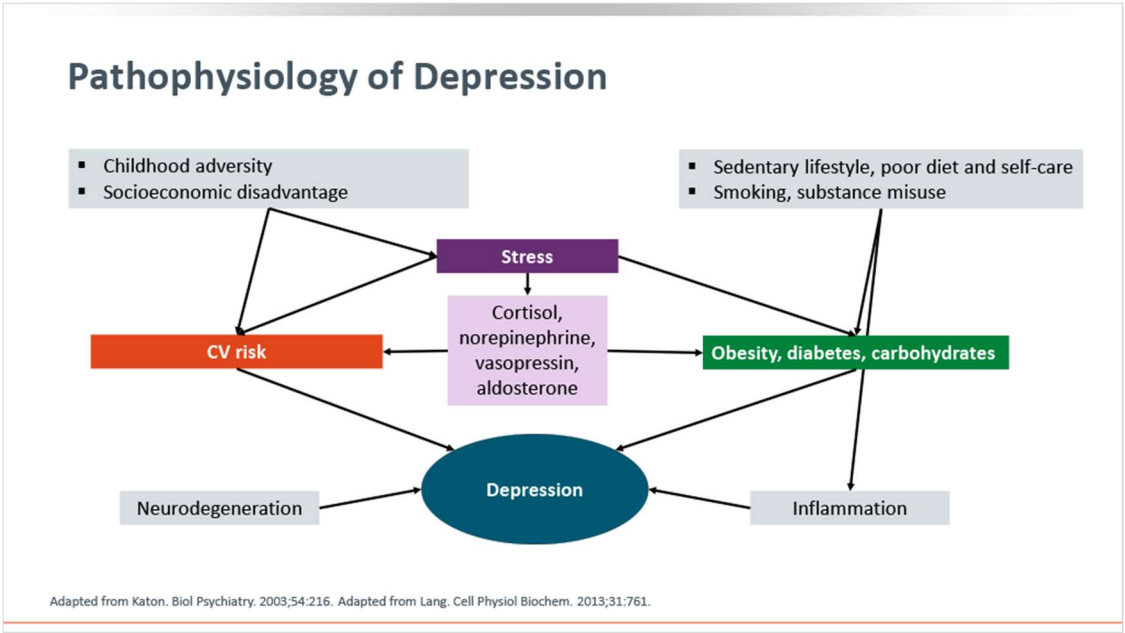
enhanced, cortisol responses in the HPA axis**(Kunugi H.)**.

RELATION BETWEEN ANS (Autonomic Nervous System) AND DD (Depressive Disorders)

It is also well-known that somatic diseases such as Addison's disease and ACTH deficiency, both of which show inadequate cortisol secretion, present psychiatric symptoms similar to MDD. These observations clearly lead to the possibility that HPA axis activity can be a subtyping marker of MDD**(Hiroshi kunugi, hiroaki Hori Shintaro Ogawa)**. The ANS is one more main player in stress reaction. Imbalance in sympathetic and parasympathetic nervous systems has been recommended in patients with MDD which could be monitored by the heart rate variability.

Excessive and attenuated activations of sympathetic and parasympathetic nervous systems, respectively, have been suggested to be underlying in the pathophysiology of MDD. In line, there is some evidence that vagus nerve stimulation is effective in treatment-resistant depression, which is closely related to the following gut micro-biota described**(Hiroshi kunugi, hiroaki Hori Shintaro Ogawa)**.

Inflammation Accumulating evidence suggests that a portion of MDD has been reformulated as a chronic inflammatory disease similar to diabetes and coronary heart disease in which pro-inflammatory cytokines such as interleukin (IL)-6), IL-1β and tumor necrosis factor-α contribute to the disease process. Elevation in peripheral pro-inflammatory cytokines leads to neural inflammation; indeed, we reported increased IL-6 levels in the CSF of patients with MDD, which was subsequently confirmed by a meta-analysis**(Andre C, Dinel AL, Ferreira G, Laye S, Castanon N).**



ROLE OF NEUROTRANSMITTERS IN DEPRESSION:

Avital mechanism of cytokine-induced depression is the activation of the tryptophan-kynurenine pathway. In line, evidence supporting the elevated activation of tryptophankynurenine pathway by using 13C-tryptophan breath test in patients with MDD. Further, it showed decreased plasma tryptophan levels in patients with MDD, which is likely to be due, at least in part, to the enhanced tryptophan-kynurenine pathway (**Priyadarshini Soni1*, Prabhat Singh2 , Lubhan Singh3 , Sokindra Kumar**). In the brain, kynurenine is transformed to quinolinic acid or 3-hydroxykynurenine in microglia, which has neurotoxic outcome through the stuff as an N-methyl-D-Aspartate Receptor (NMDAR) agonist and is thought to be involved in the pathogenesis of mental disorders.

Brain-Derived Neurotrophic Factor Several lines of evidence from postmortem studies, animal studies, blood levels, and genetic studies have suggested that BDNF is involved in the pathogenesis of depression and in the mechanism

of action of biological treatments of depression. There is convincing sign that strain decreases the expression of BDNF and that antidepressant dealings increase it. Moreover, glucocorticoid receptor interrelates with the specific receptor of BDNF, tropomyosin receptor kinase B (TrkB), and extreme glucocorticoid interferes with BDNF signaling. Altered BDNF role is involved in the structural changes and possibly impaired neurogenesis in the brain of disheartened patients. Although BDNF levels seem to be undetectably low in the human CSF, we found reduced BDNF propertied, which is produced in the processing of pro-BDNF to mature BDNF, in patients with MDD compared with healthy controls (***Hiroshi Kunugi)***.

GUT AND DEPRESSIVE DISORDERS

Another study by Colosimo et al. in this issue of Cell Host & Microbe employs a similar tactic to identify numerous bacterial metabolites that are proficient of stimulating a diverse set of GPCRs (**Colosimo et al., 2019).** This study carries out a functional screening of metabolites produced by seven different bacterial species that constitute a small group referred to as the simplified human microbiomes (SIHUMIs) (**Kovatcheva-Datchary et al., 2019**). This study also uses barr recruitment as the primary readout against more than 200 GPCRs and then follows up by purifying the selected metabolites and characterizing their chemical structures. Once again, a number of neurotransmitter receptors are found to be activated by bacterial metabolites, highlighting interplay along the gut brain axis, which is likely to have immense therapeutic implications. Furthermore, colonization of germ-free mice with SIHUMI stresses resulted in an enhancement of those metabolites, which were recognized from monocultures of these separate strains in vitro, providing a strong in vivo corollary for the findings. An interesting aspect of both studies is the identification of micro-biota metabolites as agonists for orphan GPCRs, for example, the members of adhesion GPCR subfamily such as BAI1, GPR56, and GPR97. Considering the status of GPCR deorphanization from a drug-discovery point of view, these researches have far-reaching implications and advise that looking outside the box may be key going onward. It is also vital to note that metabolites analyzed in the primary screening process are collected from specific cultures of the bacterial isolates. It is plausible that there are particular qualitative and quantitative variants in the metabolites produced by the gut microbiota under in vivo conditions, a potential aspect that can be addressed in future(**Allison Agus,1,3Julien Planchais,1,3 and Harry Sokol).** Moreover, allosteric modulation of GPCRs continues to be an intense focus of investigation from a therapeutic perspective, and therefore, it is tempting to speculate that screening the micro-biota metabolites as allosteric modulators may reveal even further surprises and interesting leads. In conclusion, these researches firmly establish a direct linking among metabolites formed by the gut microbiota and their ability to influence host bodily processes through GPCRs. Considering the widespread expression pattern of GPCRs in the body and their diverse role in human physiology, a comprehensive conceptual and experimental framework of host-micro-biome interaction may significantly contribute in GPCR targeted novel drug discovery efforts (**Shubhi Pandey,1 Jagannath Maharana,1 and Arun K. Shukla1)**. The gut microbiota produces bioactive small patch metabolites(Donia and Fischbach, 2015). exemplifications include carbohydrate derivations similar as short chain adipose acids (SCFAs), lipids similar as N- acyl amides(Cohen etal., 2017), amino acid metabolites (Dodd etal., 2017; Wlodarskaetal., 2017), and the revision of corrosiveness acids(Fiorucci and Distrutti, 2015). numerous of these metabolites impact mammalian physiology as ligands for G- protein- coupled receptors and nuclear hormone receptors (Chen etal., 2019; Colosimoetal., 2019; Venkateshetal., 2014) that could be targets for small patch medicines(Brown and Hazen, 2017) to treat and/ or help conditions similar as coronary vascular complaint(Wang etal., 2011), diabetes(Kohetal., 2018), seditious bowel complaint(Furusawaetal., 2013; Venkateshetal., 2014), and autism(Hsiao etal., 2013). The product and functionality of these motes have been demonstrated primarily in beast model systems similar as gnotobiotic mice; the applicability to mortal physiology remains to be determined (Walter etal., 2020). Interventions directed at the composition or function of the gut micro biome frequently results in larger goods in murine models than in humans whereinter-subject variability in microbiome composition is lesser. For illustration, the impact of diet on the composition of the gut microbiota is larger in mice than in humans (Baxter etal., 2019; Johnson

etal., 2019; Wu etal., 2011). Theinter -subject variability of the gut microbiota's response to diet is likely the result of complex community relations. More understanding these relations can inform the design of perfec tion diets that lead to a predictable mortal response(Johnson et al., 2019; Zeevi et al., 2015). It is believed that interactions of diet and the micro-biome influence the fecal and plasma metabiome, but this has not been well studied in humans. In some settings, diet appears to have a strong impact on the plasma metabiome independently of the gut micro-biota. For example, the plasma metabiome differs among humans consuming an omnivore or vegan diet, with only few metabolites being produced primarily by the gut micro-biota **(Wu et al., 2016).**

ROLE OF DIETARY SYSTEM:

In discrepancy, with extreme salutary changes similar as elimination of fruits and vegetables from a diet composed of either whole foods or salutary formulas, there are fairly large changes in the composition of the gut microbiota **(David et al., 2013; Lewis et al., 2015).**A study conducted by Simpson's and Shannon and found microbiome diversity were significantly higher after dietary intervention compared to baseline diversity. All significantly modulated taxa had baseline relative abundances lower than 5%, except for *Bacteroides (***Oliphant K, Allen-Vercoe E**.).

CONCLUSION:

The mortal gut microbiome is the largest endocrine organ and as similar, plays a central part in the modulation of mortal health and complaint. Given the close symbiotic relationship being between the gut microbiota and the host, it isn't surprising to observe a divergence from the normal microbiota composition(generally appertained to as dysbiosis) in a plethora of complaint countries ranging from habitual GI conditions to neurodevelopmental diseases. Mental illness contributes mainly to the global burden of disability, and to uncover new avenues for treatment, the generally tight association of neurobehavioral and metabolic dysfunction has come under violent scrutiny. The search for underlying mechanisms common to both bowel and mental illness included depressive disorders, has revealed many hormonal and neural pathways of gut-brain communication, and gut micro biota have emerged as a key node in this system. Indeed, bidirectional pathways.

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