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# MICROBES MATTER: A REVIEW ON THE CURRENT UPDATES OF GUT MICROBIOTA IN RELATION TO AUTISM

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**ABSTRACT:** Microbiota, in simple terms means the community of microorganisms, whereas microbiome means the whole genomes of the microorganisms in a particular environment. We humans consist of a large microbiome within as well as on body, most in the gut. The gut microbiota in human plays significant role in different aspects such as in human metabolism, nutrition, physiology, immune function, and various other body functions. The microbiota of human gut is mainly composed of strict anaerobes, outnumbering the facultative anaerobes. Evidence from various studies across the globe has reported that autistic people carry an altered gut microbiota in comparison to normal people, influencing the immune system thus establishing an relation between dysbiotic gut microbiota with autism. Moreover, as far as antibiotics are concerned, their irrigational use bedsides having the association with antimicrobial resistance are also associated with the autism spectrum disorder development when used in pregnancy and early childhood as reported by studies. Keeping the objective in mind, this review was written to highlight the present existing knowledge regarding gut human microbiota and its relation with development of autism and also the effect of using antibiotics in maternal life and their role in development of autism in children's.

## INTRODUCTION:

**Microbiota and Microbiome:** The term "microbiome" refers sum of microbes, their genetic information, and their ecological niche, whereas the "microbiota" means all microorganisms living in gut [1]. The human microbiome consists of a huge number of bacteria, viruses, archaea, fungi, and eukaryotic microbes residing in and on the human body [2]. Mostly the microbiota is reported from the gut.

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The gut microbiota of human is a group of microorganisms residing in the intestines of humans and are reliant with the human body. This includes more than fourty genera and four hundred to five hundred species [3, 4]. Those trillion microorganisms in the human gut live in a cooperative relationship with the host and surprisingly account for 1-2 kg of the weight of the gut [5].

The microorganisms that inhabit the gastro-intestinal tract (GIT) are estimated to be more than $10^{14}$, which means ten times bacterial cells are more as compared to human cells and almost 100 times the amount of genomic content (microbiome) [6]. The gut microbiota of humans has a significant role in metabolism, nutrition, physiology, and immune function.

The human gut microbiota mainly consists of strict anaerobes, outnumbering the facultative anaerobes. There are three phyla: the *Bacteroidetes*, the *Firmicutes,* and Actinobacteria, predominantly the other gut microbiota [1, 7]. As far as feces alone are concerned, about 2776 bacteria had been extracted which are categorized into 12 bacterial phyla [8]. The microbiota of human gut varies in composition, from delivery to adulthood. As reported in studies, initially the colonization of the gut in fetus may occur before birth in intrauterine life *via* placental colonization. Further colonization occurs during delivery *via* passage through the vagina. In caesarean section, colonization further occurs when baby comes in contact with the environment [9, 10]. Also, the proof from different examinations and surveys unequivocally shows that there is transportation of microbes and their metabolites among mother and baby by means of the amniotic fluid [11].

**Importance of the Human Gut Microbiome:** The extra genes of microbiota have added different enzymatic proteins which aren't coded by the host, thus playing an important function in accelerating metabolism of host and thus contribute to guide lining of host physiology [7]. In addition to the role of the microbiome in the transformation to complex supplements, it is likewise engaged with various other basic formative cycles, also [12]. They generate nutrients from various substrates which as usual are not digested by the host [2]. The various functions performed by gut microbes can be summarized as.

- They liberate short-chain fatty acids (SCFA) (such as acetate, butyrate, velerate, propionate, and hexanoate) from indigestible dietary fibers, which are significant wellsprings of energy for the gastrointestinal mucosa and important for shaping of immune system responses and carcinogenesis in the gut. Along with other functions, they play a role in improving glucose tolerance and insulin sensitivity [2].

- The various indole derivatives, such as indole, indoxyl sulfate, indole-3-propionic acid (IPA), *etc.*, are also important metabolites because of gut microbes, which play various important roles in the body. For example, IPA regulates intestinal barrier function, thus reducing intestinal inflammation [7].

- The gut microbe also helps in metabolizing the bile acid, thus liberating various metabolites such as deoxycholic acid and Lithocholic acid, having different roles like cell signaling, bile acid regulation, regulation of glucose, cholesterol, *etc.*, as well as antimicrobial action [7].

- They play role in the production of phenolic derivatives, which have important roles in our body, such as acting as antimicrobials, provide protection against oxidative stress, having an anti-inflammatory effect, forming erythrocytes, replicating and repairing DNA, *etc* [13].

- The gut microbe also helps in the metabolism of choline. The derivatives of choline have many important roles in the human body. [7]

- They help in synthesis of vitamins such as thiamine, folate, biotin, riboflavin, and panthothenic acid, which are also present in the diet. As per estimation approximately half of vitamin K requirement of the body daily is provided by gut bacteria [14].

- The human gut microbiota likewise assumes a part in the metabolism of polyamines such as spermidine, spermine, *etc* [7].

- The microbiota plays a significant part in the proper functioning of the host defense system (immune system), which also maintains symbiotic relationship with this wide range of microbes. This immune system-microbiota union permits the induction of protective responses to various disease-causing microorganisms as well as the maintenance of regulatory pathways which are involved in the maintenance of tolerance to various antigens [15].

**Facts about Gut Microbiota:**

- The approximate weight of human gut microbiota is 1-2.
- It evolves throughout life and is influenced by genetics, stress, diet, infection, environment and much more.

  Like fingerprints its composition.

**Microbiota-Gut-Brain Axis (GBA):** This has an important role in maintaining homeostasis.[16] This GBA is a complex, two-directional network of communication in between gut and the CNS. Different pathways like the autonomic (visceral) and enteric nervous systems (second brain), the endocrine system, the hypothalamic-pituitary-adrenal axis (HPA), body's defense system, and the microbiota, as well as their metabolites are involved in GBA. Communication between the CNS, the intestine, and microbiota occurs via this "gut-brain axis" [17].

The observation by the studies that gut shapes the GBA has put a new spark on the etiology and pathophysiology of various diseases, like depression, schizophrenia, ASD, epilepsy. Literature review also reveals, high rate of GIT diseases such as irritable bowel syndrome (IBS) among individuals suffering from migraine [18]. The gut microbiota can affect brain function as it can modulate serotoninergic, noradrenergic, dopaminergic, glutamatergic, and GABA-ergic transmission of neural signals [19].

GBA is formed by gut and brain via two directional communications between nervous, endocrine, and immune system; if there is any kind of change in any one of the organs, it affects the other organs also. Thus, any disturbance or disorder in composition or quantity of human gut microbiota has the potential to affect second brain and the CNS, suggesting that there is existence of a microbiota-GBA [20]. Studies from GF (germ-free) animals or animals treated using antimicrobials have concluded that a particular type of microbiota can impact physiology of CNS as well as neurochemistry of CNS [21]. This indicates the importance and impact of microbiota of human gut on the health of the nervous system and, most importantly, the need for further investigations in this area.

**TABLE 1: MAIN BACTERIA IN HUMAN GUT AND VARIOUS NEUROTRANSMITTER REGULATED AND SYNTHESIZED BY MICROBIOTA OF GUT AND THEIR FUNCTIONS IN THE GBA [22, 23]**

| Neurotransmitters | Antecedents` | Human Gut Microbiota | Functions in the gut-brain axis |
|---|---|---|---|
| Glutamate | Acetate | *Lactobacillus plantarum*<br>*Bacteroides vulgatus*<br>*Campylobacter jejuni* | Move gastrointestinal tactile signs to mind through the vagus nerve. |
| GABA | Acetate | *Bifidobacterium*<br>*Bacteroides fragilis*<br>*Parabacteroides Eubacterium* | This changes synaptic entry in the intestinal sensory system as well as tweaks gastrointestinal motility and aggravation. |
| Acetylcholine | Choline | *Lactobacillus plantarum*<br>*Bacillus acetylcholini*<br>*Bacillus subtilis*<br>*Escherichia coli*<br>*Staphylococcus aureus* | This directs digestive motility, emission, and intestinal chemical messanger. |
| Dopamine | Tyrosine<br>l-DOPA | *Staphylococcus* | This effects on gastric discharge, movement, and mucosal blood flow. |
| Serotonin | 5-HTP<br>Tryptophan | *Staphylococcus*<br>*Clostridial species* | This promotes motility of intestinal. |
| Tyramine | Tyrosine | *Staphylococcus providencia* | This is the precursor of octopamine. |
| Tryptamine | Tryptophan | *Staphylococcus*<br>*Ruminococcus gnavus*<br>*Clostridium sporogenes* | This actuates serotonin emission by enterochromaffin cells and furthermore advances gastrointestinal travel and various secretions of colon |

Other important microorganisms (genus) in the human gut: *Methanobrevibacter, Methanobacterium, Methanosphaera, Synergistes, Spirochaeta, Escherichia, Enterobacter, Klebsiella,* and many others.

**Autism Spectrum Disorder (ASD):** ASD, a neurodevelopmental problem is characterized by the impairment in the social interaction as well as correspondence with monotonous, confined, and stereotyped behaviors, interests, and activities [24, 25]. Roughly 1 among 100 kids is determined to have mental imbalance (ASD) all over the globe and as per the e CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network in a study covering 11 sites in the US (United States) 1 in 44 children were identified with autism [26, 27]. Though in males autism is reported to be more, but meta-analysis done, had revealed male-to-female ratio closer to 3:1 [25].

In the year 1943, Kanner wrote the first published document of ASD, a year later after a child specialist from the University of Vienna, Hans Asperger, documented about a bunch of children having almost similar behavior patterns to as Kanner [28].

Impairment in language as well as social advancement is usually noted by the parents in first three years of child's life; Symptoms can be mild, which are seen late childhood. The initial signs include joint attention, eye to eye connection, situating to verbal call, expression of face, smile as well as deficit or poor movements. The first lack of socializing may take place in half year (2-6 months) and more changes in sleeping, feeding and temperament may are seen in year one among children having risk for autism [24].

**What Makes the Scientific Community Relate Autism to the Gut Microbiome:** Evidence from various studies across the world has reported that autistic people carry an altered gut microbiota as compared to normal people, which effects body's defense system causing the secretion of its metabolites, and via this a relationship between dysbiotic gut microbiota and autism gets formed. Studies done across the globe have also related autism to various factors related to genetics, environment, intrauterine life, delivery approach, and much more, but no one has reported a particular factor. Yet the pathogenesis of autism is not fully understood. Scientists continue to find out the facts that correlate with the risk of developing autism, but no causal determinations have been made yet.

The investigations have likewise detailed that ecological gamble variables can straightforwardly impact the neuronal exercises of the developing cerebrum of the hatchling, and these natural elements are to a great extent found to shape the digestive microbiota [29]. Besides, the high predominance of gastrointestinal (GI) messes in ASD patients has provoked researchers to investigate the stomach microbiota as a putative trigger in the pathological process of ASD [8]. There are various studies done across the world that show the connection between autism and gut microbiota, such as an organic chemist at College Cork in Ireland, John Cryan, was among the primary scientists who investigated the impact of human gut microbiota on social behavior. In year 2017, he found that mice with an condition like ASD were having reduced amount of *Bifidobacterium* and *Blautia* bacteria of gut, he also reported that less tryptophan as well as bile acid were produced by their gut (these are the compounds needed for the production of serotonin, which regulates emotions and behavior). ASD youngsters have additionally been reliably found to have lower levels of gut bacteria such as *Veillonellaceae, Coprococcus*, and *Prevotella* in comparison to normal children's [30, 31].

A study done to investigate the effects of fecal microbiota transplanting gathered from ASD donators to mice has given sufficient proof which makes connection of human gut microbiota with social behavior typical of ASD [32].

Normal microbial flora, such as *Bifidobacterium infantis*, converts tryptophan present among food (precursor of serotonin) into serotonin. The bacteria, *namely Clostridium sporogenes,* increase synthesis metabolites of tryptophan known as indole-3-propionic acid (IPA). Various pathogenic microbes can invade the gut, leading to GI problems after the presence of *Clostridium bolteae.* The presence of *Clostridium* in the human colon indicates an increased risk as well as severity of autism, again a link between autism and the microbiota. Tetanus neurotoxin (TeNT) is produced by this specific strain of bacteria, which travels via vagus nerve and reaches the central nerves system, and there it blocks the neurotransmitters through proteolytic cleavage of synaptobrevin (synaptic vesicle membrane protein) and encourages entire scope of conduct shortfalls. Thus, the presence of *Clostridium tetani* can be regarded as good measure for making diagnosis of ASD [33, 34].

Literature has also noted out the bidirectional role in between human gut and brain (GBA). Proofs have also revealed a connection between modifications in the organization of the human gut microbiota, GI and neurobehavioral symptoms in children with ASD [5].

Various studies have also highlighted that dysbiosis in autism involves bacterial species as well as yeasts. Gastrointestinal *Candida albicans* is twice as plentiful in little children with ASD as compared

to ordinary people, and this can secrete ammonia as well as other toxins that induce autistic behaviors, but the role of fungi is not yet fully understood [35].

The microbiota of the human gut can influence brain function by tweaking noradrenergic, serotoninergic and dopaminergic, glutamatergic, and GABA-ergic neurotransmission. Microbiota can either impact the union and digestion of synapses or can deliver these neuroactive materials by themselves. For example, *Candida, E. coli, Enterococcus,* as well as *Streptococcus* belong to serotonin producers, while *Bifidobacterium* and *Lactobacillus* generate GABA, *Lactobacillus* generates acetylcholine, Bacillus and *Serratia* generate dopamine, and *Escherichia* and *Saccharomyces* produce norepinephrin. Luckily, because of blood-brain barrier (BBB), these as well as other neurotransmitters that are formed in the human gut cannot reach the brain (except GABA,). However, chemical messengers which are formed in human gut can have effect on the brain by acting on the efferent nervous system indirectly [18, 36].

Studies have also suggested a high level of risk of autism development for neonates and for children brought into the world by cesarean or when antibiotics (particularly penicillin or sulfonamides) were given to pregnant mothers [37].

A systemic review had reported alerted gut microbiota in ASD children with compared to that of neurotypically developed children [38].

**TABLE 2: VARIOUS MICROORGANISMS IN THE HUMAN GUT MICROBIOME AND THEIR PREVALENCE IN ASD PATIENTS [36, 39, 40]**

| Names of microorganisms | Level of microorganisms in autistic patients | Effects on autistic patients |
|---|---|---|
| *Proteobacteria* | ↑ | This causes inflammation, decrease in GSH levels, and the formation of lipopolysaccharides, (leads malfunctioning of immune system in autism). |
| *Bacteroides* | ↑ | This promotes the production of SCFAs as well as metabolites of SCFAs (propionic acid) which can affect autism behavior via the GBA. |
| *Clostridium* | ↑ | This plays role in production of endotoxins as well as propionate, associated with the seriousness of ASD symptoms. |
| *Faecalibacterium prausnitzii* | ↑ | It produces mitigating butyrate, which is viewed as valuable in children's with ASD |
| *Candida albicans* | ↑ | This outcome in the retention of sugars and the liberation of ammonia, which prompts an overabundance of GABA creation that can promote appearance of autistic behavior. |
| *Blautia* | ↓ | This plays a role in the formation of tryptophan as well as bile acid, which act as precursors of serotonin; thus, lower levels of *Blautia* leads less serotonin in the human brain which can be correlated with ASD like behavior. |
| *Prevotella* | ↓ | This have role in the metabolism of saccharides because of which ASD patients are believed having impaired metabolism of carbohydrate. |
| *Bifidobacterium (synthesizes GABA)* | ↓ | Low levels of GABA are found in children with ASD. |

GABA=gamma aminobutyric acid, SCFAs= Short-chain fatty acids ↑= Increase, ↓=Decrease

**Maternal Early-life Exposure to Antimicrobials and the Risk of Autism:** Human–microbe interactions (of beneficial microorganisms) can be altered by different ways in this era of modern lifestyle such as, urbanization and industrialization, global travel, and change in dietary habits and most important by antibiotics. The keen effects of treatment with antimicrobials on native microbiota of gut vary from the self-limiting diarrhea to pseudo membranous colitis which is serious life-threatening condition [41]. From the studies done, it is clear that antibiotics are a possible factor due to which changes in the composition of the human gut microbiota occur, which may assume a part in the ASD development. Antibiotics are the most commonly prescribed drugs during pregnancy, accounting for 40–60% of all prescribed medications during this period [742, 43].

As the microbiome of mother shapes the microbiome of baby, exposure to antimicrobials in

pregnancy as well as in early life is assumed to affect the biodiversity of microbiome in a child, directly as well as indirectly via changes in the microbiome of mother. This can also affect metabolism, bone growth, and functioning of immune system. It also may have potential effects on the developing GBA and behavior of child [44]. The various studies have been done to find an relationship between the use of antimicrobials in early-maternal period and the risk of ASD development, such as;

A study revealed that use of antimicrobials was connected with an increased risk of ASD odds ratio (OR) = 1.16, 95% confidence interval (CI) 1.09–1.23 in childhood. Moreover, in a study, they also reported that early-life exposure with antimicrobials showed a much stronger connection with ASD (OR = 1.46, 95% CI 1.38–1.55). In simple terms, they concluded that maternal and early-life antimicrobials have connections with higher risk of ASD and ADHD in infancy [44].

A systemic review and meta-analysis were done, including nine studies published up to february 2019. Their analysis has also concluded that early antimicrobial, as well as including pre- and postnatal exposure of antimicrobial, significantly increased the autism risk in children. In simple terms, their results indicated a relationship between autism and early antimicrobial exposure, specifically that maternal exposure to antimicrobial is an important risk factor for ASD in children [45].

**Role of Probiotics and Prebiotics in the Human Gut Microbiome and ASD:** The worldwide probiotics market has developed quickly, which makes probiotics a well as a food besides a supplement. Probiotics have been used as a health-promoting factor for a very long time. Probiotics, as defined by FAO/WHO 2001, are living micro-organisms which when administered in sufficient amounts, induce health benefit in the host [46, 47]. Probiotics helps to improve overall health as well as immunity. As already discussed, the role of human gut microbiota in development of various metabolic diseases as well as neurological diseases like ASD we have tried to explore the role of probiotics in the human gut microbiome and ASD. Probiotics are used regularly to raise the balance of the internal gut microbiota in order to maintain and improve GI health in humans. Microbial dysbiosis, a typical issue of the ongoing time, is brought about by microbial contaminations, changes in diet, and anti-microbials. Curiously, probiotics are one of the critical answers to reestablish gut microbial equilibrium and prevent infectious disease in individuals after anti-microbial treatment, which prompts gut microbiota dysbiosis. Antibiotic-Associated Diarrhea (AAD) is a typical severe impact of anti-microbial treatment that outcomes from the interference of the gastrointestinal microbiota. Various studies have reported that *Lactobacillus rhamnosus* as well as the *Saccharomyces boulardii* were the most defensive against AAD [48].

The seven core genera of microorganisms which are mostly used in probiotic products are *Lactobacillus (e.g., L. acidophilus, L. rhamnosus), Bifidobacterium, Saccharomyces (e.g., S. bulgardii*), *Streptococcus, Enterococcus, Escherichia,* and *Bacillus (e.g., Bacillus coagulans*) [49, 50].

Glenn Gibson introduced the concept of prebiotics for the first time in 1995. In the sixth meet of the International Scientific Association of Probiotics and Prebiotics (ISAPP) (2008), probiotics were defined as “dietary prebiotics” as “a selectively fermented ingredient that results in specific changes in the composition and/or activity of the GI microbiota, thus conferring benefit to host health”. In simple terms, they are food ingredients which are non-digestible and benefit the host by selectively restoring the growth and/or activity of one or more number of microorganisms in gut thus improving host health. The various types of probiotics used are fructans, galacto-oligosaccharides, starch and glucose-derived oligosaccharides, pectin, non-carbohydrate oligosaccharides, *etc* [51, 52].

Regarding probiotic and prebiotic use in ASD, the literature was searched from the PubMed database, which revealed a total of 4 results for meta-analysis, of which only two were related to the topic. Interestingly, no meta-analysis was found in the PubMed database before 2020. A meta-analysis conducted had concluded that probiotics and prebiotics didn't essentially work on the seriousness of ASD patients, GI issues, or comorbid

psychopathology in ASD and the outcome is disconnected to the past writing [53]. Another meta-analysis was done by concluding that the literature involved gave restricted proof to the viability of probiotics on youngsters with ASD [54]. Both studies also revealed that the studies included for meta-analysis had small sample sizes with/or shorter durations of intervention, different probiotics were used, and poor quality of research.

**CONCLUSION:** We are now in an era where we humans can modify health through food, measure the effects through our microbes or metabolites, and edit genes. We are going towards an era where microbes can be used as fingerprints to identify a person. We have mostly seen microbes as foes; now we should change this perspective and accept them as friends as well. With the research done till now, we have got a lot of information regarding the role of microorganisms in health and disease. There is obviously a need to conduct more and more research in order to understand them and use them as markers for identifying the various diseases with unknown etiology such as autism. The better we figure out the associations between the human host and the microbiota, the more chances there are to develop new diagnostic, prognostic, as well as therapeutic capabilities for the benefit of the human race.

The expansion in the quantity of examinations in various regions of the planet offers novel open doors for progressing logical disclosure of chemical imbalance etiology while at the same time extending local area ability to address neglected needs, particularly among underserved populaces. The use of metabolomics approaches has extraordinarily progressed how we might interpret instruments connecting stomach microbiota synthesis and action to wellbeing and sickness. As far as antibiotics are concerned, their irrigational use is not only associated with antimicrobial resistance, but the evidence of their relation to ASD is also in front of us. This signifies the importance of taking antibiotics under the proper supervision of clinical pharmacists. As probiotics and prebiotics are concerned about whether they have a positive impact on ASD, the review concludes that there is a further need for studies with longer intervention and durations, good RCT designs, and other studies that might be more likely to reveal the effects of probiotic treatment in improving ASD-related behavioral symptoms.

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