International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 11; Issue 08 (B); August 2022; Page No.1425-1433
DOI: http://dx.doi.org/10.24327/ijcar.2022.1433.0317

Research Article

DIVERSITY OF GUT MICROBIOTA AND DYSBIOSIS IN INDIAN POPULATION

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A R T I C L E I N F O

Article History:

Received 06th May, 2022
Received in revised form 14th June, 2022
Accepted 23rd July, 2022
Published online 28th August, 2022

A B S T R A C T

Gut microbiome is a complex set of microorganisms present in human gastrointestinal tract. Microbiota is important for the health of an individual as they are involved in the immune homeostasis, metabolism of carbohydrates, lipids and amino acids and their correlation with the pathogenicity of various diseases. In this review, we emphasized on the diversity of gut microbes present in Indian population The major microorganisms found in the gut of the Indian population are *Prevotella, Firmicutes, Bacteroidetes, Bifidobacterium* and *Faecalibacterium*. This review focuses on the diversity of gut microbiota of Indian population into 4 regions (north, south, east and west) with various gut microbiota studies. Microbiome diversity found in different regions of India are mainly due to geographical and habitat variations, dietary habits, socio-economic status, lifestyle and climatic variations. Dysbiosis of gut microbiota and their association with various disease in reference to Indian population has also been considered in this review.

INTRODUCTION

The gut microbiota is a set of complex group of microorganisms harbouring the human gastrointestinal (GI) tract (Thursby & Juge. 2017). The number of microorganisms that are present within the GI tract exceeds the value of 10^{14} (Bäckhed *et al*. 2005). The gut microbiota is considered to affect the individual's health and wellness. The gut microbiota is helpful in maintaining and development of host immunity and it has also a role in metabolism of xenobiotic (Pushpanathan *et al*. 2019). The altered gut microbiota or the dysbiosis state is found to be associated with various pathogenic conditions like inflammatory bowel disease (IBD) (Khan *et al*. 2019), cardiovascular diseases (Tang *et al*. 2017), chronic kidney diseases (Plata *et al*. 2019), type 2 diabetes (Gurung *et al*. 2020), and cancers in the gastrointestinal tract like gastric, colorectal cancer etc (Gagnière *et al*. 2016; Meng *et al*.2018).

The gut microbiota varies in different groups among Indian population. The microbiota diversity depends on various factors like diet, ethnicity, environmental conditions, habitat or geographical conditions, genetic profile and age (Pulipati *et al*.2020). The main microorganisms in gut microbiota of healthy Indian population found in the "Landscape of Gut Microbiome-Pan India Exploration" (LogMPIE) were *Faecalibacteriumprausnitzii* and *Prevotellacopri*.

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This review summarizes the diversity of Indian gut microbiota between the four regions i.e. north, south, east and west India. Subsequently this review has also aim to highlight the association of dysbiosis with various disorders like tuberculosis, colon cancer, inflammatory bowel disease (IBD), malnutrition, celiac disease and autism in Indian population.

Microbiota diversity in Eastern parts of India

In this section, we discussed various studies from eastern states consists of Manipur, and West Bengal.

A study by Tuikhar *et al* analysed gut microbiota in young adults and centenarians. In centenarians, biodiversity and higher species richness within the family *Ruminococcaceae* was reported. As unclassified species *Ruminococcaceae* D16 among family appeared as a common longevity signature. Among herbivorous and omnivorous animals, *Ruminococcaceae* D16 has been reported as major butyrate producer which is a fundamental metabolite for gut health and immune system homeostasis. Higher levels of butyrate might be one of factor involved in preventing immunosenescence and inflammation. Higher richness of carnivores associated butyrate producer, *Peptostreptococcacaee* and *Fusobacterium* were reported. This might be linked to traditional dietary habits as study subjects were heavy meat eaters. Known butyrate producers within the Bacteroidetes phylum, *Rikenellaceae* (*Alistipes*) and *Porphyromonaceae* (*Parabacteroides, Odoribacter, Porphyromonas*) were

reported. Gut microbiota of centenarians might be supplemented in various metabolic pathways for production of butyrate. *Desulfovibrio* was reported as an extreme aging trait. Contribution of sulfur compounds in longevity can be investigated as *Akkermansia* and *Alistipes* are promoted by sulfur compounds and *Alistipes* and *Odoribacter* produces sulfonolipids. Decrease in richness of *Prevotella* species was observed in centenarians. This might be due to fact that *Prevotella* has lowest genetic potential to produce short chain fatty acids and carbohydrate active enzymes and their abundance has also been linked with chronic inflammation. *Christensenellaceae* and *Bifidobacterium,* considered as longevity bacteria did not show any significant variation. In young adults, higher abundance of *Faecalibacterium* was reported which might indicate as microbiota signature of youthfulness. *Erysipelotrichaceae* dominance was reported which is involved in host lipid metabolism. This is an alert for population as *Erysipelotrichaceae* are associated with inflammation-related disorders and colorectal cancer (Tuikhar *et al*. 2019).

Another study by Gosh *et al* investigated gut microbiome diversity of children from Birbhum district of West Bengal. Impaired nutritional status was found due to abundance of likely pathogenic microbial groups and depletion of various commensal genera like *Roseburia, Faecalibacterium, Butyrivibrio, Eubacterium* and *Phascolarctobacterium. Roseburia and Butyrivibrio*short chain fatty acids producers whereas *Faecalibacterium, Roseburia* and *Eubacterium* have anti-inflammatory properties. Depletion of these species might be linked with the low- grade inflammation, onset of inflammatory bowel disease and malabsorption of nutrients. With the decrease in nutritional status, there are chances of increase in functional interdependence among the various microbes of the gut (Ghosh*et al*. 2014).

Table 1 describes detailed microbiota diversity in eastern region of India.

mainly breast-feeding and weaning. There was no significant impact on faecal microbial communities' abundance due to cessation of breast feeding by 3 months but exclusive breast feeding was found to be associated with higher *Enterobacteriaceae* abundance (Kabeerdoss *et al*. 2013).

Another study by Dhakan *et al* showed higher abundance of species from genera *Bifidobacterium*, *Ruminococcus*, *Clostridium*, and *Faecalibacterium* in population of Kerala. Study population consumed an omnivorous diet with rice and animal-based products. *Bacteroides* and *Clostridium* abundance was associated with the omnivorous diet.Higher levels of short chain fatty acids were found which might be due to an omnivorous diet (Dhakan *et al*. 2019).

A study by Ramadass *et al* compared the gut microbiota of Jawadhi hills tribal population and rural population in Vellore. Both the groups followed distinct dietary habits as tribal individuals relied much on millets-based diet, daily pork intake and no milk consumption whereas rural individuals consumed rice-based diet, meat once in a week and milk. Firmicutes were in abundance in both the groups which might be due to their diet which includes mainly cereals providing poorly absorbed carbohydrates. This phylum includes *Ruminococcus, Roseburia* and *Faecalibacterium* and all of these are short chain fatty acids producers. Other members of this phylum were *Lactobacillus, Veillonella* and *Streptococcus* which are beneficial via metabolic and immune effects. Proteobacteria was more abundant in rural subjects and included various facultative anaerobic organisms and pathogens which might be due to contaminated drinking water, increased oxygen tension in colonic lumen and frequent gastrointestinal infections. Actinobacteria was also more abundant in rural subjects and Bifiobacterium was main component. This might be due to consumption of dairy products and fruits which contains galactooligosaccharides and fructooligosaccharides (Ramadass *et al*. 2017).

Table 1 Gut microbiota diversity in eastern states of India

S.No	Authors	No. of study subjects	Region	Gut Microbiota	Dominating factors
1	Tuikhar *et al*. 2019	Centenarian = 30 Internal young control = 30 External young control = 30	Manipur High centenarian prevalence group Low centenarian prevalence group	*Ruminococcaceae, Peptostreptococcacaee, Fusobacterium, Bacteroidetes, Rikenellaceae (Alistipes) and Porphyromonaceae (Parabacteroides, Odoribacter, Porphyromonas)* Decrease in richness of *Prevotella* *Faecalibacterium*	Age
2	Ghosh *et al*. 2014	n = 20	West Bengal Decreased nutritional Index Increased nutritional index	Increase in *Escherichia, Shigella, Enterobacter, Proteobacteria, Streptococcus, Vellonella,* and *Leuconostoc* Decrease in*Butyrivibrio, Roseburia, Eubacterium, Mitrosuokella, Phascolaractobacterium, Synergistetes, Dialister, Faecalibacterium, Succinatimonas*	Nutrition

Microbiota diversity in Southern parts of India

In this section, we included various studies from the southern states of India which consists Tamil Nadu, Kerala, Telangana and Karnataka.

A study done by Kabeerdoss *et al* analysed microbiota in faeces of infants in Tamil Nadu at various time points after birth. Counts of faecal bacteria showed peak by the 4th day and was constant in first 6 months of life. There was no significant increases in faecal bacterial count after 1stday, indicating very fast colonisation to peak levels just after birth. Faecal microbiota showed variation between vaginally delivered and caesarean delivered infants indicating association between the gut colonisation pattern and socio-economic status of mainly,

Balamurugan *et al* tried to find age related changes in gut microbiome. It was assured that the study population was homogenous and followed homogenous dietary pattern so that no variation was there in study subjects with respect to diet. Continuous and gradual change in the faecal microbiota after early childhood were found which continues into adolescence and adulthood. Changes with the age were shown by quick decline in *Lactobacillus* in preschool children. Changes in adolescence were increase in *E. rectale* and *F. Prauznitzii* and along with *Bacteroides*, these are the main producers of short chain fatty acids and essential to colonic physiology. *Bifidobacterium sp.* were maximum in 2-3y age group and declined steeply in adulthood which might be a matter of concern as these are known for use as probiotics and might be

helpful in the maintenance of good health. Bifidobacteria may be a target for the nutritional strategies for their conservation as they inhibit enteric bacterial pathogen growth and prevent gastroenteritis (Balamurugan *et al.* 2008).

A study by Kabeerdoss *et al* analysed the gut microbiome of vegetarian and omnivorous females from Tamil Nadu. *Clostridium* cluster XIV a bacteria (short chain fatty acids producers) and butyrate-producing bacteria were in abundance in omnivorous which might be due to complex-microbiota-microbiota interactions or dietary constituents which are not measured in this study (Kabeerdoss *et al*. 2012).Tang *et al* explored comparative characteristics of gut microbiota in women from the Democratic Republic of the Congo (DRC) (Equateur Province) and South India (Belagavi, Karnataka). The study concludes that diet has a stronger association of gut microbiota as compared with demographic characteristics. The families of bacteria with the greatest abundance relatively were *Prevotellaceae* (29%), *Ruminococcaceae* (18%) and *Lachnospiraceae* (20%). All these families include species that can degrade complex polysaccharides and considered potent short chain fatty acid producers. *Ruminococcus* was higher in DRC as compared to Indian population because of higher intake of animal flesh foods in DRC population. *Succinivibrio*, another possible short chain fatty acid producer was also found to be associated with high fiber diets and was considered to be positively associated with protein intake i.e. dietary intake in India and fish/ insects in DRC. Gut microbiota richness is associated with mainly omnivorous diet, and were higher in DRC subjects as compared to lactovegetarian Indian population (Tang *et al*.2019).

Table 2 describes detailed microbiota diversity in southern region of India.

Microbiota diversity in Western parts of India

Some studies from western states like Maharashtra and Gujarat are discussed in this section. Pandey *et al* studied differences in microbiota diversity between vaginally and Caesarean section delivered infants from Pune, Maharashtra. Between the gut microbiota of vaginally and caesarean section born infants, distinct differences were found at day 7 as vaginally delivered infants had lower species richness at day 7.*Acinetobacter sp.* were most abundant in vaginally delivered infants which might be acquired from their stay out of the hospital as vaginally delivered infants spends less time (1 or 2 days) in the hospital as compared to caesarean section infants (Pandey *et al*.2012).
Tandon *et al* analysed gut microbiota of urban cohort from Ahmedabad. Most of study subjects were from lower socio-economic background and had local dietary habits focusing on carbohydrates and fibre rich components. The study concluded that western India specific cluster had higher chao value conferring a higher richness of microbiota as compared to other geographies. Western Indian samples were also appeared to be highly enriched in bacterial genera that encodes functions associated with xenobiotic degradation and metabolism, biosynthesis of secondary metabolites and amino acid metabolism. Western India gut microbiota indicates a *Prevotella* dominated community given a fibre and carbohydrate rich diet (Tandon *et al*. 2018).

Another study by Chaudhari *et al* analysed gut, oral and skin microbiome individuals who belonged to 6 various patrilineal related three generation families who stayed together in rural areas of Pune. *Prevotella* was in abundance in both oral and gut microbiome which is consistent with the plant based-carbohydrates rich diet.

Table 2 Gut microbiota diversity in southern states of India

S.No	Authors	No. of study subjects	Region	Gut Microbiota	Dominating factors
1	Kabeerdoss*et al.* 2013	n=83	Tamil Nadu 1. First week 2. After day 3 3. After day 4 4. Around 6 months 5. 1st day to 6 months 6. Vaginally delivered infants • Birth to 90 days • At day 90	 *Enterobacteriaceae* *Bifidobacteria* *Staphylococci* *Bacteroides–Prevotella* group and *C. coccoides–E. rectale* *Enterococci* *Bacteroides–Prevotella* Bifidobacteria	Age and mode of delivery
2	Dhakan*et al.* 2019	n = 57	Kerala	*Bifidobacterium*, *Ruminococcus*, *Clostridium*, and*Faecalibacterium*	Diet
3	Ramadass*et al.* 2017	• Jawadhi hills tribe = 10 • Rural = 10	Vellore, Tamil Nadu 1. Jawadhi hills tribal population 2. Rural population	• *Firmicutes, Proteobacteria, Bacteroidetes and, Clostridium* • Low *Actinobacteria, Enterobacteriaceae and Streptococcus Firmicutes, Proteobacteria, Bacteroidetes* and *Actinobacteria*	Diet
4	Balamurugan*et al.* 2008	• 2–3 y = 16 • 4–5 y = 17 • 6–7 y = 23 • 8–9 y = 19 • 10–11y = 9 • 12–13y = 12 • 14–15y = 16 • 16–17y = 18 • 28–50 y = 30	Vellore, Tamil Nadu 1. 2-3yrs old 2. More than 6 yrs old 3. 6-9 yrs old 4. Adolescents and adults	*Bifidobacterium* and *L. acidophilus* *E. rectale* *F. prausnitzii* *Bacteroides-Prevotella-Porphyromonas*	Age
5	Kabeerdoss *et al.* 2012	• Vegetarian = 32 • Omnivorous = 24	Tamil Nadu	*C. coccoides–E. rectale* group higher in the omnivorous	Diet
6	Tang *et al.* 2019	• Democratic republic of Congo (DRC) = 117 • Karnataka = 100	Karnataka	*Succinivibrio, Roseburia, Prevotella, Bifidobacterium, Lactobacillus and Ruminococcus*	Diet

In the oral microbiome, high abundance of aerobic (*Neisseria)*, facultative anaerobic (*Streptococcus)* and obligate anaerobic (*Prevotella*) bacteria indicates the oxygen role in structuring the composition of bacterial diversity for healthy oral cavity. Higher abundance of *Dialister* in the study population along with the dietary fibre consumption should be tested for possible association as these bacteria are known for short chain fatty acids production. In the 1st generation members, *Succinivibrio* (higher fiber degrading potential) and *Ruminococcus* were abundant. Short chain fatty acids producers, *Dialister* and *Phascolarctobacterium* and *Megasphaera* having unique and diverse CAZymes were in abundance in 2nd generation members whereas *Prevotella, Bifidobacterium*, and *Bacteroides* were higher in 3rd generation (Chaudhari *et al*. 2020).

An analysis was done by Marathe *et al* to elucidate age related differences in gut microbiome and enrolled 2 families. 3 individuals were selected from the same family which meant there were less chances of genetic variation and study subject were staying in the same house which further lowered the variations due to environment and feeding habits. Consistent decreases in *Firmicutes/Bacteroidetes* with the increasing age was found and this trend was different from the European population (Marathe *et al.* 2012). Statistical validity of this study is limited as it involved only 6 individuals which decreases probability of finding generalized gut microbiome differences with age in study population.

Table 3 describes detailed microbiota diversity in western region of India.

Study conducted by Bamola *et al* assessed gut microbiota of vegetarian and non-vegetarian subjects from Delhi. Eight subjects from both the groups were taken into consideration. Vegetarian diet included plant-based product milk and dairy products while eggs, meat/fish consumption were added in non-vegetarian diet. High calorie diet and milk consumption along with plant polysaccharides intake might be the reason for high Firmicutes proportion as compared with Bacteroidetes in vegetarian subjects. Consumption of animal protein diet with low plant polysaccharide intake in longer term leads to decrease in Firmicutes level and increase in bile-tolerant organisms like Bacteroidetes. High animal based proteinaceous diet consumption by non-vegetarian subjects justifies the *Prevotellaceae* dominance (Bamola *et al*. 2017).

Das *et al* explored diversity of gut microbiome of 3 distinct communities which included rural Leh, rural and urban Ballabhgarh. *Prevotella* was found to be dominant in Leh region whereas Ballabhgarh had high amount of Proteobacteria, mainly *Vibrio*, and *Pseudomonas*. The diet of Leh subjects was rich in animal protein whereas diet of Ballabhgarh subjects was rich in plant associated components. *Prevotella* showed a cohort-independent association with a non-vegetarian dietary pattern. *Collinsella* was found to be abundant in subjects using ghee. *Roseburia*and *Sporobacter* were associated with subjects using mustard and sunflower oil as cooking oil. Gut microbiota of Ballabhgarh subjects had high abundance of genes belonging to several xenobiotic pathways which might be due to high exposure of individuals to industrial or agricultural chemicals.

Table 3 Gut microbiota diversity in western states of India

S.No	Authors	No. of study subjects	Region	Gut Microbiota	Dominating factors
1	Pandey *et al*. 2012	• Vaginally born infants = 12 • Caesarean section born infants = 12	Pune 1. Vaginally delivered infants	*Staphylococcus haemolyticus, Lactobacillus ruminis, Streptococcus salivarius, Streptococcus parasanguinis, Acinetobacter pittii, A. junii A. baumannii, Ochrobactrum intermedium, Bifidobacterium longum sub sp. infantis, Bifidobacterium bifidum and Bifidobacterium breve*	Mode of delivery
			2.Caesarean section delivered infants	*Roseomonaspecuniae*, *Paracoccus* sp., *Enterococcus* sp., *Streptococcus vestibularis*, *Chryseomicrobiumimtechense*, *Staphylococcus* sp., *Clostridium difficile, Citrobacter sp. and E. coli*	
2	Tandon *et al*. 2018	n = 80	Ahmedabad	*Bacteroidetes*, *Firmicutes. Proteobacteria* (*Succinivibrio, Sutterella*), *Actinobacteria* (*Bifidobacterium), Prevotella, Alloprevotella, Bacteroides, Faecalibacterium, and Roseburia*	Ethnicity
3	Chaudhari *et al*. 2020	n = 54	Pune 1. Gut microbiome	Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Tenericutes, *Prevotella*, *Dialister*, *Bacteroides*, *Megamonas*, *Succinivibrio*, *Faecalibacteriumand Ruminococcus*	
			2. Oral microbiome	*Proteobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Actinobacteria, Neisseria, Streptococcus, Prevotella, Porphyromonas, and Haemophilus*	
4	Marathe *et al.* 2012	n = 6	Pune 1. Children 2. Adult	*Fecalibacterium*, *Roseburia, Streptococcus and Weissella* *Dialister*, *Prevotella, Fecalibacterium and Roseburia*	Age

Microbiota diversity in Northern parts of India

Northern states discussed in this section includes Madhya Pradesh, Delhi, Jammu and Kashmir, Himachal Pradesh and Haryana. Dhakan *et al* analysed gut microbiota of healthy individuals from Bhopal district of Madhya Pradesh. Overrepresentation of *Prevotella* might be associated with carbohydrates rich diet. Other genus *Lactobacillus, Megasphaera*, and *Mitsuokella* presentation might be due to higher consumption of dairy products and fermented food along with the carbohydrates rich diet. Higher serum branched chain amino acid levels which have role in promoting Type 2 Diabetes and insulin resistance were reported (Dhakan*et al*. 2019).

The similarity among the three population studied was remarkable (Das *et al*. 2018). A study from Himachal Pradesh by Attri *et al* analysed the lactic acid producing bacteria (LAB) and Bifidobacterium diversity. During the 1st month of life, higher richness index was reported for LAB and bifidobacterial group which decreased in 2nd month which might be due to the fact that LAB are dominant in healthy vagina and it is assumed that LAB are present in vaginally delivered infants. Dominance of *Bifidobacteria* and other groups like *Bacterioides-Prevotella* and *Clostridia* during 2nd month might be associated with the LAB decrease. Higher diversity of LAB and bifidobacterial group might be due to breast feeding only as breast milk is rich in LAB and

Bifidobacterium. It is also reported that breast milk contain prebiotic factors like human milk oligosaccharides (HMOs), antimicrobial properties. HMOs are found to increase the bifidobacterial growth (Attri*et al*. 2018).

Table 4 describes detailed microbiota diversity in northern region of India.

Table 4 Gut microbiota diversity in northern states of India

S.No	Authors	No. of study subjects	Region	Gut Microbiota	Dominating factors
1	Dhakan *et al*. 2019	n = 53	Bhopal	*Prevotella*(*P. copri* and *P. stercorea*) and *Megasphaera*	Diet
2	Bamola *et al*. 2017	• Vegetarian subjects = 8 • Non-vegetarian subjects = 8	Delhi 1. Vegetarian subjects	Firmicutes followed by Bacteroidetes and Family *Ruminococcaceae*	Diet
			2. Non-vegetarian subjects	Bacteroidetes followed by Firmicutes and family *Prevotellaceae*	
3	Das *et al*. 2018	• Leh = 35 • Rural Ballabhgarh = 25 Urban Ballabhgarh = 24	1. Leh, Ladakh 2. Ballabhgarh a. Both rural and urban	• *Bacteroidetes, Prevotella, Roseburia* • *Bacteroides, Vibrio, Eggerthela* and *Pseudomonas* • *Bifidobacterium, Sporobacter and Gemmiger* • *Coprococcus, Clostridium, Ruminococcus, Howardella, Erysopelotrichaceae and Peptococcus* • *Collinsella*	Diet
			b. Urban	*Lactobacillus, Bifidobacterium, Sporobacter and Gemmiger Pseudomonas*	
4	Attri *et al*. 2018	n = 10	Himachal Pradesh	*Enterococcus sp., Streptococcus sp.* and *Lactobacillus sp. Bifidobacterium breve, B. animalis*subsp. *lactis*, *B. choerinum* and *B. pseudolongum*	Age

Miscellaneous Studies

This section includes studies in which more than 3 sample sites were taken into consideration or discussed the Indian gut microbiota in Indian population as a whole. Kaur *et al* analysed gut microbiome diversity from three different geographical locations i.e Scur Buchan village in Ladakh, Jammu and Kashmir, PipliyaBuzurg village in Khargone district, Madhya Pradesh and Khuri village in Jaisalmer district, Rajasthan. Significant differences in the gut microbiome composition of the study subjects from various regions was reported. No correlation was found between the genus and diet, location and age (Kaur *et al*.2020). Another study by Bhute *et al* investigated gut microbiota diversity from Pune and Delhi. In the study subjects, extensive inter-individual variations were suggested in gut microbial communities which were characterized by *Prevotella* and *Megasphaera* dominance. *Prevotella* dominance might be a result of Indian diet as these microbes are involved in degradation of complex plant polysaccharides. *Lactobacillus* and *Bifidobacterium* dominance can be justified due to high consumption of fermented food by Indian population. *Megasphaera* found in study subjects is involved in production of short chain fatty acids (Bhute *et al*. 2016).

A subsequent study by Deheingia *et al* tried to describe gut microbiota diversity in tribal population of eastern states. They included healthy volunteers from Assam, Sikkim, Manipur and Telangana. Participating subjects mainly consumed rice with variation in vegetable, meat, legumes, fish, fruit and tubers consumption whereas milk product consumption was high in Sikkim tribes. Diet of Indian tribes is rich in carbohydrates and dietary fibres. Tribes from Assam and Telangana had similar gut bacterial profile. All the tribes had higher carbohydrate metabolizing bacteria which may produce short chain fatty acids like butyrate. Tribes of Sikkim had more *Actinobacteria,* mainly *Bifidobacterium,* which has been reported to be involved in maintenance of immune system, protection against pathogens and exertion of nutritional effects to intestinal cell and host (Dehingia *et al*.2015).

A comparative study by Singh *et al* which tried to find a correlation between gut microbiota and lifestyle induced changes between urban and tribal population. This study has tried to analyse the impact of urbanization on human gut microbiota. The tribal cohort had higher diversity as compared to gut microbiota. Higher Bacteroidetes were found in urban cohort. These *Bacteriodetes* are associated with high fat and protein diet. Higher *Firmicutes* were found in rural cohort and these are considered to be associated with production of beneficial metabolites like the short chain fatty acids, helping in maintaining gut's integrity. *Prevotella* had higher dominance in urban population as compared to rural. This study also performed functional interface analysis and found the abundance of predicted functions such as lipopolysaccahride biosynthesis in urban population, which is a marker of low-grade systemic inflammation in the human body which might be due to dysbiosis and compromised gut barrier function. Functional analysis in tribal population found predictive abundance of propanoate metabolism, which has considered to have anti-lipogenic, cholesterol lowering and anti- inflammatory effects (Singh *et al*. 2019). Kumbhare *et al* worked on comparative analysis of gut microbiota diversity of small cohort of Indian and Finnish children. *Megasphaera* and *Prevotella* was found to be predominant in Indian children. This study also suggests an influence of α-1,2-fucosyl transferase and mode of delivery on gut microbiota (Kumbhare *et al.* 2017). Landscape of Gut Microbiome-Pan India Exploration or Log MPIE study by Dubey *et al* is first factorial parallel group design study to record nationwide diversity of gut microbiome. This study was conducted at 14 different geographical locations from north (4), south (3), east (3) and west (4) India. They employed V3-V4 region of 16sDNA sequencing using Ion one Touch 2 system and Quantitative Insights Into Microbial Ecology (QIIME) workflow was used

for analysis. *Prevotellacopri* and *Faecalibacteriumprausnitzii* were reported as most dominant organism in Indian gut microbiome (Dubey *et al*. 2018).

Alteration in Gut Microbiota and Their Association with Various Diseases in Indian population

Various factors like diet, antibiotics, alcohol, lifestyle, age, gender, immunodeficiency, and host genetics affect homeostasis of gastrointestinal microbiome. Both increased and decreased microbiome diversity as well as fluctuations in bacterial diversity leads to dysbiosis which might be associated with various health disorders. Alteration in gut microbiota is found to be associated with various diseases like obesity, undernutrition, inflammatory bowel disease, Colorectal carcinoma, Non-alcoholic fatty liver disease, Liver cirrhosis, Type 1 diabetes, Type 2 diabetes, Atherosclerosis, Autism spectrum disorder, Cardiovascular disease, tuberculosis and neurodegenerative disorders in various populations (Maji *et al*. 2018; Das & Nair 2019). In Indian population, some studies have also tried to find correlation between altered gut microbiota and various disorders. Patil *et al* studied dominant gut microbiota of obese, lean, normal and surgically treated obese individuals of Indian origin. *Bacteroides* were found to be dominant in obese and surgically treated obese subjects and these bacteria are known to be associated with ulcerative colitis and some species produces faecapentaenes which is an in vitro mutagen. Butyrate producers, *Faecalibacterium* were low in obese individuals whereas these bacteria have beneficial effect on the gut health and this decrease of this bacteria might be a risk factor for inflammatory disorders of gastrointestinal tract in obese individuals. High archael density and increased faecal short chain fatty acids were found in obese subjects (Patil*et al*. 2012).

Gaike *et al* explored gut microbiota of newly diagnosed diabetics (New DMs), pre-diabetics (Pre DMs) and diabetics on antidiabetic treatment (known DMs) and compared with healthy individuals who were non-diabetics (ND). In New DMs, lower number of observed operational taxonomic units (OTUs) were found which shows an increase in Known DMs on antidiabetic treatment. Loss of bacterial diversity was observed in disease condition but antidiabetic treatment was found to help in regaining the bacterial diversity. Rare taxa were high in Known DMs which suggested that altered diversity of rare taxa may have an important role in structural and functional aspects of gut microbiome after antidiabetic treatment. High and low abundance of *Prevotella* in ND and New DMs might be a distinct biomarker for diabetes in Indian population (Gaike *et al*. 2020). Pushpanathan *et al* studied gut microbiota dysbiosis in type 2 diabetes (T2DM) and compared with non-diabetic individuals. In T2DM, Proteobacteria was found to be slightly abundant and this is a potential diagnostic marker of risk of disease and dysbiosis. *Escherichia* was found to be dominant in T2DM and shows positive correlation with HbA1c and BMI. In T2DM, some species of *Lactobacillus* might contribute to chronic inflammation but *Lactobacillus sp.*were not studied in this study. Gram negative bacteria were higher in T2DM which was correlated with the high levels of lipopolysaccharide and high insulin resistance in T2DM (Premalatha Pushpanathan *et al.* 2016). Another study investigated eubacterial, eukaryotic and archaeal dysbiosis in gut microbiome of long-standing diabetics (Known DMs) and New DMs and compared with healthy subjects. Members of *Lachnospiraceae* and *Ruminococcaceae* are producers of short chain fatty acids which provides many health benefits and in the study subjects, decreasing trend of these families was observed with the progressive deterioration of glucose tolerance. Loss of SCFAs producers and decrease in abundance of *P.copri* in New and Known DMs might be associated with the glucose tolerance as these microbes showed negative correlation with fasting glucose. Abundance of fungi was also increased as new DMs were reported to be enriched in fungal pathogens like *Candida, Aspergillus* which might be due to poor glycemic control (Bhute *et al*. 2017).Das *et al* explored association of gut dysbiosis with T2DM and diabetic retinopathy (DR) and compared with healthy subjects. Decrease in short chain fatty acids producers like *Lachnospira* might have role in diabetes. In T2DM, anti-inflammatory bacteria were decreased whereas increase in pro-inflammatory bacteria was found. Reported increase in *Escherichia* was applicable to development of diabetes as amyloid producing E.coli and their phages are known to be associated with autoimmunity and protein misfolding which are one of the possible pathological pathways of diabetes progression. For the onset of DR, chronic inflammation is a prerequisite. Various anti-inflammatory genera were found to be decreased. Increased inflammation in DR subjects was attributed to the decrease in anti-inflammatory bacteria rather than pro-inflammatory bacteria increase. In the gut microbiome of subjects of both DR and T2DM, it was found that probiotic, anti-inflammatory, and bacteria which could be pathogenic were decreased in comparison with healthy subjects and these changes were more marked in DR patients (Das *et al*.2021).

A study by Gupta *et al* compared the gut microbiome of healthy and malnourished children. Gut microbiome of malnourished child was interrupted as abnormal gut microflora which leads to various disorders characterized bymoderate malabsorption and inflammation. Various events like unchecked bacterial proliferation, disruption in community dynamics of commensal intestinal flora, concurrent infections and impaired immunity follows the continuous aberration of gut microbiome. This study indicated high abundance of enteric pathogens which are recognized to cause intestinal inflammation causing malabsorption. More such studies are required to establish any relation in gut microbiome dysbiosis and malnutrition in Indian population as this study only included 1 healthy and 1 malnourished child (Gupta *et al*. 2011).Huey *et al* studied gut microbiome of undernourished children living in slums of Mumbai. Study subjects were undernourished with the high proportion of nutrient deficiency and poor growth and Proteobacteria was reported as the major taxa in their gut microbiome. High Proteobacteria abundance has been known as a marker of dysbiosis and is associated with the negative health outcomes. Most of the species were classified as *Gammaproteobacteria* which has been found in premature infants with necrotizing enterocolitis (Huey *et al*. 2020).

A study by Maji *et al* investigated the gut microbiota alteration in tuberculosis (TB) patients as compared with the healthy subjects. Microbial dysbiosis was found to be associated with the active TB infection and bacterial diversity showed an increase in diversity in TB patients even after a month of antibiotic administration. TB patients had increased *Firmicutes/Bacteroidetes* ratio which is known to affect the short chain fatty acids concentration. It was concluded that increase in short chain fatty acids producers might not be

beneficial in all the health conditions and more studies are required to understand the dynamic role of short chain fatty acids producers in various dysbiotic conditions like obesity and TB. Loss of appetite is seen in TB patients hence leading to decreased intake of carbohydrates and dietary fibre causing selection of *Bacteroides* over *Prevotella* in TB patients. Increased abundance of propionate and butyrate producers like *Phascolarctobacteriumsuccinatutens*, *Roseburiainulinivorans* and *Faecalibacteriumprausnitzii* were reported in TB patients which resulted in decreased vitamins and amino acids biosynthesis. Other pathobionts like *Shigella sonnei*, *E. coli*, *Streptococcus pneumonia* and *Streptococcus vestibularis* were reported to be increased in TB patients (Maji *et al*.2018).

Pulikkan *et al* studied gut microbiome dysbiosis in children with autism spectrum disorder (ASD). No significant difference was found in the diversity of faecal microbiota of healthy and ASD children. Certain short chain fatty acid producers like *Faecalibacterium* and *Roseburia* were found to be decreased in ASD children which assist the hypothesis that lower short chain fatty acid levels in ASD leads to an imbalance in brain functioning and behaviour. High abundance of *Lactobacillus* in ASD children directs towards its association with autism. However, it is still not clear whether *Lactobacillus* abundance is a cause or effect of ASD (Pulikkan *et al*. 2018). Dinh *et al* tried to characterize microbiota diversity in children with stunt growth. Gut microbiome of stunted children was found to be dominated by inflammogenictaxa while probiotic bacterial species were reported to be abundant in healthy children (Dinh *et al.* 2016).

Bodkhe *et al* investigated gut microbiome of first-degree relatives (FDRs) of patients of celiac disease (CeD), control subjects and CeD patients. Genetically susceptibility of FDRs to CeD might offer a chance to explore gut microbiota in pre-disease condition. At the amplicon sequencing variant (ASV) level, significant differences indicates that specific bacteria such as *Helicobacter* might be important for the CeD pathogenesis. In FDRs, high abundance of ASVs of potentialbeneficial bacteria mainly those belonging to short chain fatty acid producer genera indicated that they might have protective role in CeD development. Less number of ASVs were differentially abundant between the diagnosis group in faecal sample as compared to duodenal biopsies. This fact indicates that more disrupted microbiota is present at the disease site as compared to faecal microbiome (Bodkhe*et al*. 2019).Human stomach is also not a sterile organ, it also contains various microbes. One of most common infection of stomach is *Helocbacter pylori* infection. *H.pylori* infection is linked with various disease like chronic/atrophic gastritis, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, adenocarcinoma and duodenal ulcers. Das *et al* tried to find effects of *H.pylori* infection of gut and stomach microbiota. Biopsy from endoscopic mucosa of antrum and corpus of patients with *H.pylori* infection was analysed resulting in negative association between abundance of *H.pylori* and microbial diversity (Das *et al*. 2017).

Bamola *et al* studied gut microbiome of colon carcinoma and Inflammatory Bowel Disease (IBD) patients and compared with healthy subjects. Gut microbiota dysbiosis has been observed in IBD patients. Reduction was found with respect to *Firmicutes*. Abundance of phylum *Verrucomicrobiota* in IBD patients was found. There was no net increase in *Actinobacteria* and *Proteobacteria*. *Verrucomicrobiota* is found to rarely increase in case of mucosal inflammation. *Lactobacilli* was also dominant in healthy individuals which give a fact that lack of *Lactobacilli* might be associated with increased gut mucosa inflammation of gut microbiota. Pathogenic species of *Clostridium* was also found in colon cancer samples (Bamola *et al*. 2017).

Figure 1 depicts profile of gut microbes reported in various disease conditions.

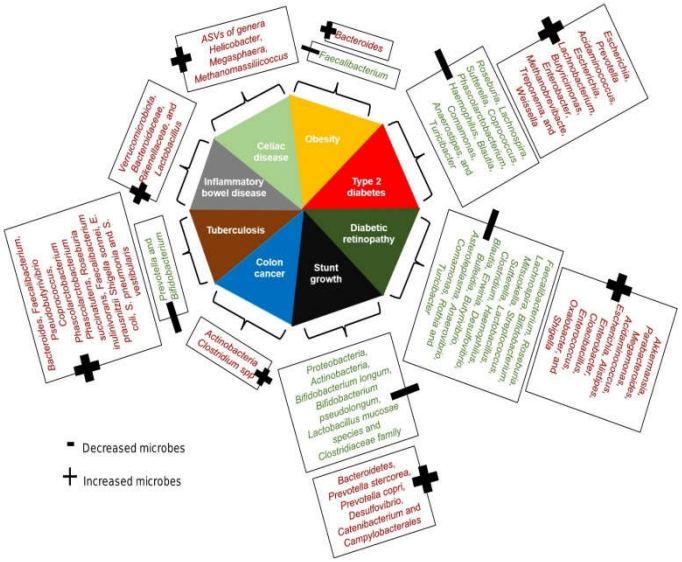

Fig 1 In various physiological disease, either some microbes are increased or decreased abruptly leading to dysbiosis

CONCLUSION

Diversity of Indian gut microbiota is very dynamic and complex. Major organisms in Indian gut microbiota includes *Prevotella, Firmicutes, Bacteroidetes, Bifidobacterium* and *Faecalibacterium*. In northern region of India, the major organisms found were *Bifidobacterium* and *Bacteroidetes* while in southern region *Bifidobacterium* and *Prevotella*. In eastern region, *Faecalibacterium* and *Dialister* were most commonly found whereas *Actinobacteria* and *Streptococcus* in western India. Change in gut microbiome between the regions arises because of heterogeneity due to geographical and habitat variations, dietary habits, lifestyle, socio-economic status and climatic variations. Due to this complexity of gut microbiota, a large multi-centered study with large sample size should be used to define the core gut microbiota.

Alteration of gut microbiota in disease has been an intensive topic of research because of connection of gut microbiota with various diseases pathogenesis and its correlation with immune homeostasis. In Indian population, some studies have tried to conclude these alterations in gut microbiome. Diseased conditions included in this review are diabetes, diabetic retinopathy, malnourishment, tuberculosis, autism spectrum disorder, stunt growth, celiac disease, inflammatory bowel disease and colon cancer. As this data is very limited, large studies are still required to define this alteration of gut microbiota in many unexplored conditions.

This review provides information to researchers on diversity of core gut microbiota in different regions of India. This review also provides insight to health care professionals about involvement of gut microbiota in pathogenesis of disease or alteration in immune homeostasis during a diseased state.

Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

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How to cite this article:

Nikita Sandhu *et al* (2022) 'Diversity of Gut Microbiota and Dysbiosis in Indian Population', *International Journal of Current Advanced Research,* 11(08), pp. 1425-1433. DOI: http://dx.doi.org/10.24327/ijcar.2022.1433.0317

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