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Preliminary Study on Factors Leading to Inflammatory Bowel Disease

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Abstract: ***Study of microbiome is a prevalent area of research. Inflammatory bowel disease (IBD) is a group of intestinal disorder caused by impaired human gut microbiome. Although sex, age, diet, genetics, and lifestyle are important predisposing factor for IBD, the exact cause of it is still unclear. A short-term study was carried using digital survey method to understand the cases and factors leading to IBD in India. It was observed that human diet, age, sex, ethnicity, and family history are responsible for formation of ulcers, a form of inflammatory bowel disease.***
Keywords: Microbiome, ulcers, Sex, Age, Diet, Genetics, Lifestyle

I. INTRODUCTION

Our diet controls the supply of food for microorganisms residing inside our body. Thus, what we eat impacts the formation of our gut microbiota. The microorganisms inhabiting our gastrointestinal tract constitute the most complex ecosystem in the body. Studies have reported their quantity to be between 10^{12} to 10^{14} cells/gram of various species of microbes. This microbial community plays an important role in human digestion and promoting health. They also help in preventing colonization from harmful pathogens and maintain immunity. [1] The entire microorganisms present in our body is called the human microbiome. The term microbiota is used to refer to the types of organisms present in a habitat. The human microbiome consists of different microbiota that colonizes different habitats of the body. For example, the microbiota colonizing the skin is different from that of the gut, but they are all part of the human microbiome. A complete analysis of the human gut microbiome is important to understand the exact mechanisms by which the gut microbiota is involved in health and disease. Development of microbiota in the human gut begins after birth. The foetus is sterile until birth. Following vaginal delivery or caesarean, microbes from the mother and environment start rapidly colonizing the intestinal tract and other body parts. Later, feeding mode plays an important role in kinds of microbes getting inoculated inside the body. Breastfed milk contains the mother's antibodies and commensal microorganisms such as Bifidobacterium spp and Lactobacilli spp. Whereas, formula-fed infants have a low level of these bacteria. Factors such as environment and hygiene measures also play an important role in the type of microbes inhabiting the body. [2]

The seeded microbes start developing for the first few years of life. Further, the composition of the microbial community becomes more adult-like. These microbes mainly belong to archaea, bacteria, fungi, and protozoa. Besides, these microbes carry 1000 times the gene as compared to microbes residing outside our body surface. These microbes essentially inhabit all the mucosal surfaces with the gastrointestinal tract being colonized by high densities of microorganisms which are collectively known as gut microbiota. Microbial density reaches 10^4 to 10^7 cells/gram in the jejunum and ileum and 10^{11} cells/gram in the colon. It is dominated by five bacterial species namely Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomirobia. [3] Table no.1 depicts dominant species of micro-organisms present in the human body. The microbial diversity of the human microbiome has been mapped using 16S rRNA gene sequencing and metagenomic analyses as major tools in several national and international microbiome research efforts. Table no.2 depicts tools used to study human microbiome, and Figure no. 1 depicts different levels of analyses in human microbiome study.

Table 1: Dominant species of micro-organisms present in human as microbiota.

Sr. No.	Dominant species	References
1	Bacteroidetes spp and Firmicutes spp.	[4]
2	Bacteroidetes spp, Firmicutes spp and Actinobacteria spp.	[5]
3	Bacteroidetes spp, Parabacteroidetes spp, Ruminococcus spp, Dialister spp, Bifidobacteroidetes spp, Lactobacillus spp and Butyrivibrio spp.	[6], [7]
4	Bacteroidetes spp, Faecalibacterium spp, Bifidobacterium spp, Actinobacteria spp, Provotella spp and Ruminococcus spp.	[8], [9]
5	Bacteroidetes spp, Firmicutes spp, Actinobacteria spp and Proteobacteria spp.	[1]
6	Mucor spp.	[10]

Table 2: Tools used to study human microbiome.

Sr. No.	Techniques used to study microbiome	References
1	Spectroscopic methods.	[11]
2	Culture independent metagenomic analysis.	[12]
3	Human intestinal tract chip analysis.	[6]
4	16 S rRNA encoding, Sanger sequencing and Pyrosequencing.	[9]
5	Metagenomics.	[13]
6	Single nucleotide polymorphisms, Metagenomics and 16S rRNA encoding.	[1]
7	Internal transcribed spacer (ITS) based sequencing.	[14]
8	MALDI-TOF	[10]
9	16S rRNA sequencing using 454FLX technology and QIIME pipeline.	[15]

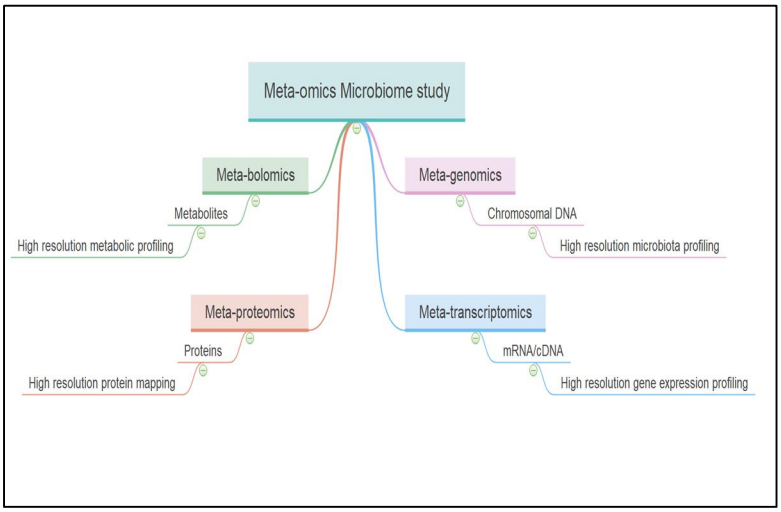

Fig 1: Different levels of analyses in human microbiome study.

Gut design varies among herbivores, carnivores, and omnivores. The guts of herbivores have an extra compartment separated from stomach expected to microbial aging of ingested plant material. Conversely, omnivorous people have just the stomach before the digestive tracts. The human gastrointestinal tract holds a core microbiome that is from the ingested oral microbes and is ruled by species of Bacteroidetes (Prevotella), Firmicutes (Streptococcus, Veillonella, Lactobacillus), Actinobacteria (Propionibacterium), Fusobacteria, and Proteobacteria (Haemophilus, Methylobacterium). [4]

The colon is important part of digestive organ. In the colon, bacteria are available in huge numbers. Facultative aerobes such as *Escherichia coli* is present here. The facultative aerobes devour any remaining oxygen, delivering the digestive organ anoxic. Anoxia commit development of anaerobes micro-organisms such as Clostridium and Bacteroides species.

During the entry of food through the gastrointestinal tract, water is egested from the processed material, which slowly is removed through excrement. Microbes make around 33% of faecal matter. An individual sheds around 10^{13} bacterial cells every day through faeces. [16]

Even though there is high fluctuation of micro-organisms from individual to individual in gut population, a specific person has moderately steady flora for long time. Three general gut enterotypes have been depicted, varying fundamentally by the advancement of one microbial gathering in each enterotype. Enterotype 1 is enriched in Bacteroides spp, enterotype 2 is enriched in Prevotella spp, and enterotype 3 is enriched in Ruminococcus spp. The association of an individual with an enterotype seems to be affected with nutrition, and ethnicity. Each enterotype is functionally distinct; for example, they differ in their capacity for vitamin and enzyme production. Thus, diet contributes to the health or disease status in a person. [17], [18]

The gut flora changes with respect to sex, age, diet, lifestyle, medication, etc. Change in this results in diseases related to digestive system. Inflammatory bowel disease (IBD) is the inflammation of digestive tract resulting in various damaged to digestive system.

It is a group of intestinal disorder. Inflammation in digestive tract disturbs the normal digestion process. IBD is very painful and destructive and can be life threatening. The parameters of IBD varies depending upon the severity of inflammation. Mostly the person suffers from bleeding ulcers and diarrhoea, which occurs when affected parts of the bowel can't reabsorb water. Stomach pain, cramping, and bloating is also observed due to bowel obstruction. Potential weakness, weight loss and anaemia is observed in individuals with IBD. Malnutrition complicates and increases the severity of IBD. In extreme cases the person may suffer from colon cancer, fistulas, intestinal perforation, etc. IBD shock is usually caused by loss of blood during a long, sudden episode of bloody diarrhoea. Although may factors can predispose IBD, the exact cause is still unclear. [7], [19] The main objective of this survey was to study the factors associated with IBD in India.

II. METHODOLOGY

A digital survey was made using google form. Information about age, sex, smoking habits, nutrition intake, lifestyle, ethnicity, clinical symptoms of ulcer, family history, and medication was gathered. The results were process to obtained graphical understanding about IBD in Indian population.

III. EXPERIMENTAL RESULTS

Inflammatory bowel disease is associated with formation of ulcers in digestive tract. Frequency of passing stool increases with abdominal pain and cramps. Sex, diet, lifestyle, and medication are some of the predispose factors for IBD. 246 responses were recorded from digital survey. The key findings are discussed, and recommendations are provided for future research.

1) *Age:* IBD affects people of all ages, with a peak incidence between 15 and 30 years old, and a second peak occurring in elderly subjects. The individuals of interest for the purpose of this study were from 10 and above age groups. As per age distribution, individuals in age group of 10 to 18, 19 to 30, 31 to 45, 46 to 59 and above 60 were consider as adolescence, youth adults, middle aged adults, old age adults and senior citizens respectively.[20] In the present study, less cases of ulcers were reported in individuals of 10 to 18 group and above 46 age group. Focus on healthy food and home-made food may be the reason for this. More individual of 19 to 30 age group had ulcers followed by that in 31 to 45 age group. This may be because of individual preference to eat junk and fast food. This bring in changes with gut microorganism which result in ulcer formation. Figure no. 2 shows the scenarios explained here. Diagnosis for ulcer formation was conducted by Hsiao and *et al* in 2014 for individual ranging from 7 to 77 age with a median of 25 years. 53% patients were with ulcerative colitis, 12% have proctitis, and 54% have extensive colitis. Of the patients with Crohn's disease, 31% have ileal disease, 33% have colonic disease, and 33% have ileoco lonic disease, and 2% have isolated upper gastrointestinal disease. 76 of the 85 patients were of European ancestry. [18], [21]

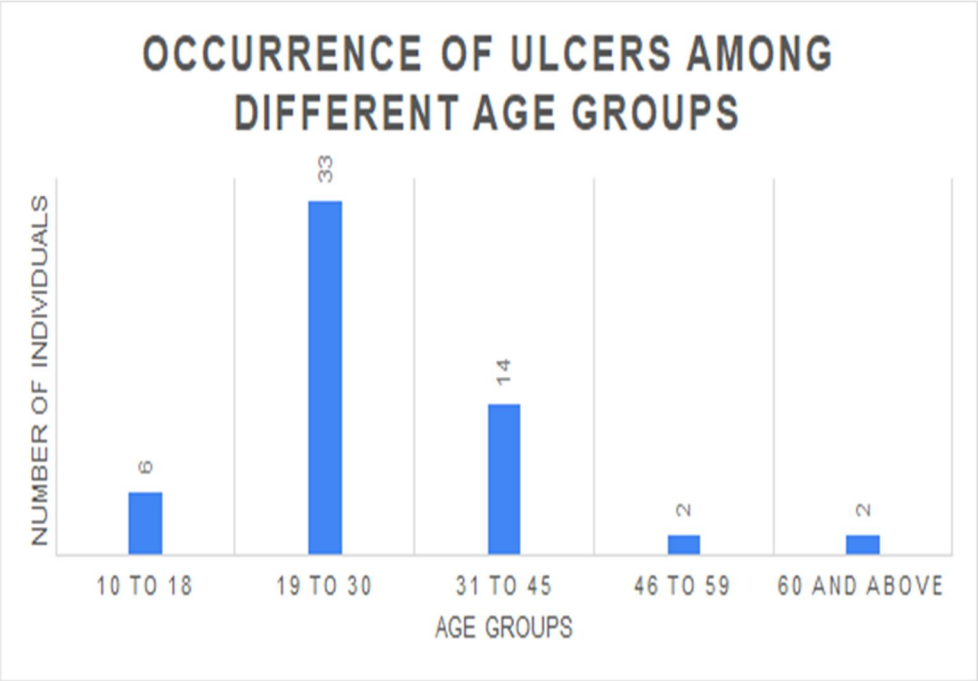

Fig 2: Occurrence of ulcers with respect to age.

2) *Gender:* Composition of human gut microbiota is also influenced by sex. The appearance of disease conditions and drugs also modulates microbiome composition and activities. In general, IBD affects both genders equally. However, ulcerative colitis is more common among men, while Crohn's disease is more common among women. [22] In the present study, from the survey results it can be observed that males are prone more to ulcers in India than females. Peak of the incidence is between 19 to 30 age group individuals. In this group it was observed that males and females are equally suffering with ulcers. Gut microbiota of 82 people was examined by Dominianni and *et al* in 2015. Gut microbiome in ladies had lower amount of Bacteroidetes spp. than men. Basal metabolic rate was also higher in this females than males. Presence of higher amount of these bacteria in females was associated with sex steroid hormones levels. [15]

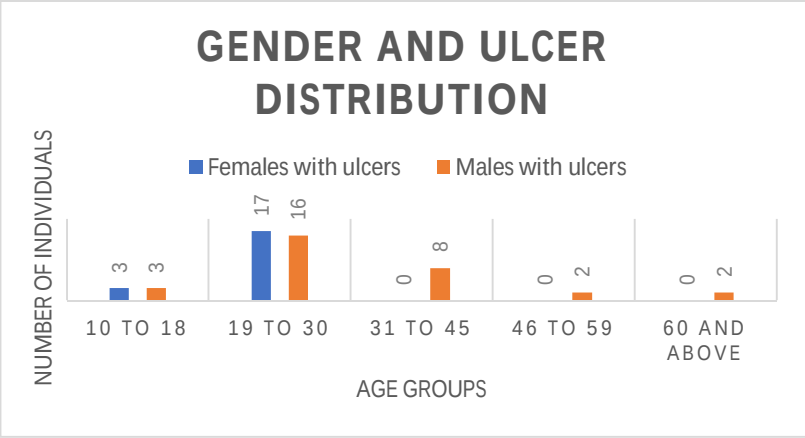

Fig 3: Occurrence of ulcers with respect to gender.

3) Smoking: Smoking is one of the main risk factors for developing IBD. Smoking also aggravates the pain and other symptoms of Crohn's disease and increases the risk of complications. In the present study, no such effect was observed.

4) *Ethnicity:* IBD can occur among all population. However, certain ethnic groups have a higher risk. In the present study, it was observed that individuals from west zone have more chances of ulcers than other zones of the country. (Figure no. 4) People who live in urban areas and industrialized countries have a higher risk of getting IBD. Those with white collar jobs are also more likely to develop the disease. This can be partially explained by lifestyle choices and diet. People who live in industrialized countries tend to eat more amount of processed food. A transgenic approach to link gut microbiota was used by Li, Wang, and *et al* in 2008. Different techniques like the spectroscopic method, microbiomic and multivariate statistical analysis was used to analyse faecal and urinary samples. At the species level, structural differences in gut microbiota of the Chinese family and American family were reported. Overall, in both populations, Firmicutes and Bacteroidetes species were reported. However Chinese individuals had Bacteroidetes to Firmicutes ratio ranging from 0.26 to 1.36. Overweight families had the lowest Bacteroidetes to Firmicutes ratio. Gender-specific differences were also observed. Bacteroidetes and Prevotella group were more prominent in males. [4]

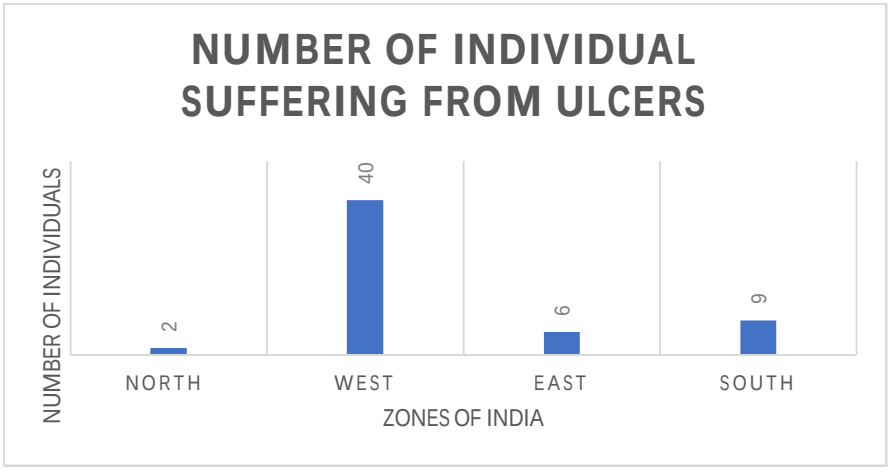

Fig 4: Occurrence of ulcers with respect to ethnicity.

5) *Diet:* Diet and nutritional status are the most important determinants of human health. As per the records received from survey it is seen that individuals with high carbohydrate intake have ulcers than other component in diet. (Figure no. 5) To study occurrence of ulcers based on diet, Peter turnbaugh and *et al* in 2009 created an animal model of the human gut ecosystem by transplanting fresh or frozen adult human faecal microbial communities into germ-free C57 BL/6J mice. They used culture-independent metagenomic analysis. The Diet of these mice was shifted from a low-fat plant polysaccharide-rich diet to a high-fat high sugar wester diet. They observed that humanized mice fed with a Western diet have increased adiposity. Firmicutes, Bacteroidetes, and Actinobacteria were present as dominated phyla. [5] Gaboriau and *et al* in 2003 reported that a single bacterial species alone cannot help to give protection to human gut infection rather sequential bacterial colonization is required. Oral tolerance was studied in adult gnotobiotic mice colonized with human faecal microflora. [23] In addition to a number of beneficial roles, the gut microbiota has been reported to be involved in various diseases such as obesity, diabetes, inflammatory bowel diseases, etc. The gut composition of 123 non-obese and 169 obese Danish individuals was studied. The low richness of gut microbiota was reported in obese individuals with inflammatory bowel diseases.[6] Intestinal microbiota alterations in obese subjects are associated with local and systemic inflammation suggesting that the obesity related microbiota composition has a pro-inflammatory effect. Faecal microbiota of 28 subjects were analysed by biophylogenetic profiling microarray. Faecal Calprolectin and plasma C reactive protein levels were determined to evaluate intestinal and systemic inflammation. Decrease Bacteroidetes / firmicutes ratio increases inflammation. Plasma C reactive protein levels have also increased in this subjects . [24]

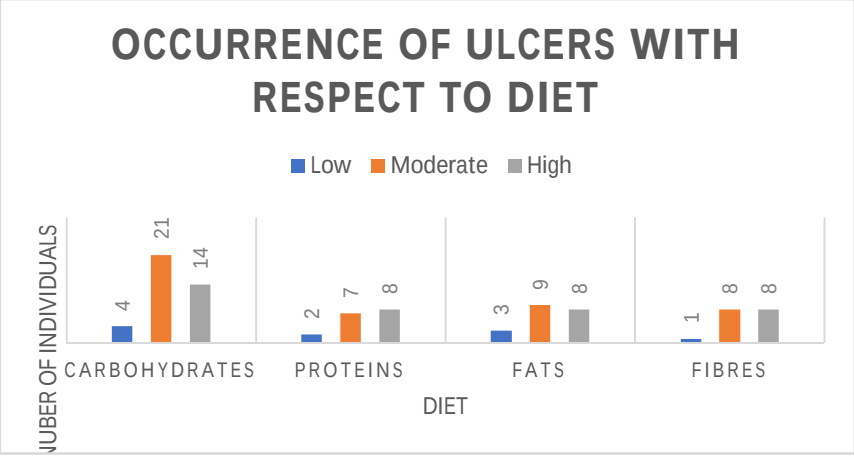

Fig 5: Occurrence of ulcers with respect to diet.

6) *Family History:* The gut microbiome is affected by multiple factors including genetics. Bonder and *et al* in 2016 have addressed the influence of host genetics on microbial species in 1514 individuals. Single nucleotide variation was seen with Bifidobacterium genus. 33 genomic loci were observed in gut microbiomes having different microbial pathways. The strongest taxonomical association was observed for genus Blautia and Methanobacteriaceae. Bacteria of Blautia genus are immunogenic epithelial barrier associated microbes linked to abnormal paneth cell count, Crohn's disease and primary sclerosing cholangitis. It was also observed that LINGO 2 gene of them has been associated with body mass index, obesity, and motion sickness. Methanobacteriaceae species have been linked with an increase in body mass index and lipids levels. Individuals with higher levels of *Dialister invisus* showed diet dependent improvement in their inflammatory and cytokine profiles. [13] However, Rothschild and *et al* in 2018 have reported that the gut microbiome is not significantly associated with genetic ancestry and the host genetics have a minor role in determining microbiome composition. He examined genotype and microbiome data from 1046 individuals with several distinct ancestral origin who share a common environment. [1] In the present study, among the people suffering from ulcers, 18 have diarrhoea, 14 suffered from abdominal pain and 12 had unintended weight loss issue too despite feeling hungry all time. 12 had frequent stool passing issues. Further, these issues were prevalent with other members in their family and thus it may be considered as genetic cause.

7) *Drugs:* Under some pathological conditions such as acute diarrhoea illness and antibiotic treatment, depending on the host physiology and diet, the individual microbiota can be depleted. The reduction has negative effects on the host well-being and can be associated with a higher susceptibility to enteropathogenic infection. In the present study no effect of drugs was recorded.

IV. CONCLUSION AND FUTURE WORK

The study and findings were totally based on the data obtained through the survey. It is observed that human gut microbiome is influenced by diet, age, sex, ethnicity, and family history. However, there is a need to collect more data to come at firm conclusion. Detailed parameters leading to ulcers and related disease should be studied. Studying microbiome through clinical samples can support the finding by providing experimental proof.

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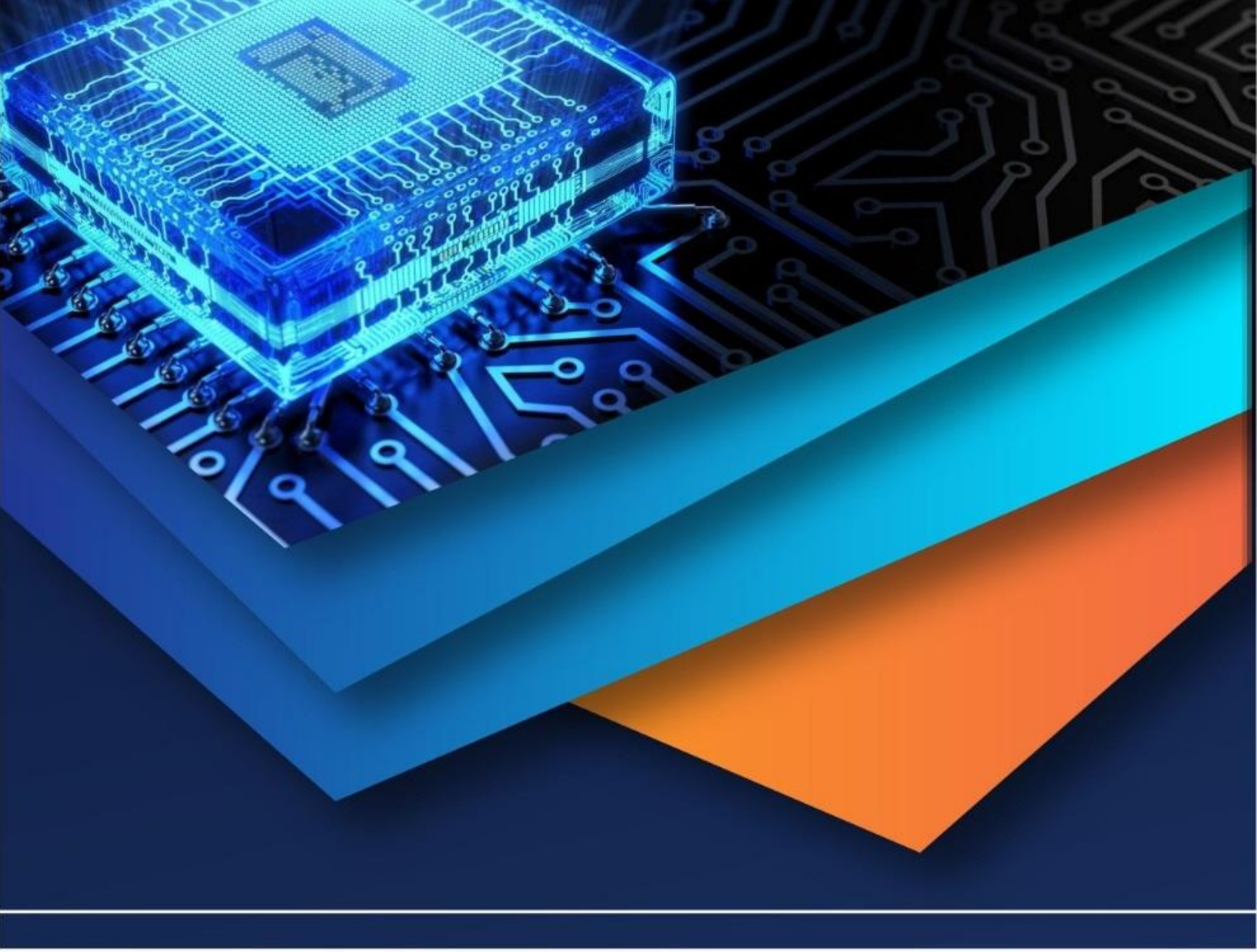

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