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# Characterization of gut microbiota profile in Iranian patients with bipolar disorder compared to healthy controls

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**Introduction:** The human gut microbiota plays a crucial role in mental health through the gut-brain axis, impacting central nervous system functions, behavior, mood, and anxiety. Consequently, it is implicated in the development of neuropsychiatric disorders. This study aimed to assess and compare the gut microbiota profiles and populations of individuals with bipolar disorder and healthy individuals in Iran.

**Methods:** Fecal samples were collected from 60 participants, including 30 bipolar patients (BPs) and 30 healthy controls (HCs), following rigorous entry criteria. Real-time quantitative PCR was utilized to evaluate the abundance of 10 bacterial genera/species and five bacterial phyla.

**Results:** Notably, *Actinobacteria* and *Lactobacillus* exhibited the greatest fold change in BPs compared to HCs at the phylum and genus level, respectively, among the bacteria with significant population differences. *Ruminococcus* emerged as the most abundant genus in both groups, while *Proteobacteria* and *Bacteroidetes* showed the highest abundance in BPs and HCs, respectively, at the phylum level. Importantly, our investigation revealed a lower *Firmicutes/Bacteroidetes* ratio, potentially serving as a health indicator, in HCs compared to BPs.

**Conclusion:** This study marks the first examination of an Iranian population and provides compelling evidence of significant differences in gut microbiota composition between BPs and HCs, suggesting a potential link between brain functions and the gut microbial profile and population.

## KEYWORDS

bipolar disorder, gut-brain-axis, gut microbiota, mental disorder, qPCR assessment

## 1 Introduction

Psychiatric disorders are behavioral or mental disorders, which cause discomfort or disruption in personal, occupational, and social activities and have significant consequences for the patient's life (Bolton, 2013). The life expectancy of individuals with these disorders is one to two decades shorter than that of healthy people (Hennekens et al., 2005; Kupfer, 2005; Nordentoft et al., 2013; Lomholt et al., 2019). Studies have shown that the prevalence of psychiatric disorders varies in different countries, depending on factors, such as welfare, level of education, and income (Demyttenaere et al., 2004).

According to the World Health Organization (WHO), one in four people experience at least one mental disorder in their lifetime, with bipolar disorder (BD) being one of the most severe ones (Demily et al., 2009; Holtz, 2017; Painold et al., 2019). A systematic review conducted in 2007 showed that the prevalence of mental disorders is 29% in Iran, which is almost 11.4% higher than the global rate (Taheri Mirghaed et al., 2020). The WHO also reported that the lifetime prevalence of BD is 1% to 2% around the world. Generally, BD is recognized as a type of mood disorder, characterized by neurological and psychiatric problems and immune and physiological imbalances (Marwaha et al., 2013; Kaplan et al., 2014). Bipolar Disorders (BD) are now recognized as a multidimensional and intricate condition, influenced by a myriad of factors, encompassing age-related physiological alterations, substance misuse, temperament traits, and susceptibility to stressful life events, as substantiated by their notable associations with alcohol and drug dependence, alongside cigarette smoking (Wilens et al., 2008; Chauvet-Gélinier et al., 2012; Mutz et al., 2022).

The prevalence of mental disorders is high in different countries, and the significant cost of rehabilitation and treatment is a major challenge (Christensen et al., 2020). Following the COVID-19 pandemic, the prevalence of these disorders has increased significantly in recent years, emphasizing the importance of these disorders (Chekole and Abate, 2021; Khademi et al., 2021; Li Y. et al., 2022). There have been persistent efforts to find new ways to diagnose and treat BD, and several methods have been proposed (Culpepper, 2014). However, this disorder is still classified and recognized by its phenotypic characteristics, and there is no verified biomarker to distinguish bipolar patients (BPs) from healthy individuals (Chen et al.; Lichtenstein et al., 2009; Van Snellenberg and De Candia, 2009).

Recently, considerable attention has been paid to the analysis of human microbiota as a promising biomarker to diagnose and treat BD (Dickerson et al., 2017). The gut microbiota imbalance is associated with metabolic disorders (e.g., diabetes and obesity), irritable bowel syndrome, celiac disease, gastrointestinal inflammatory disease, and neurodegenerative diseases (Sampson et al., 2016; Rodrigues-Amorim et al., 2018). Bowel and digestive disorders, including irritable bowel syndrome, colitis, and celiac disease, are also prevalent complications in people with mental disorders (Severance et al., 2015). Additionally, digestive disorders are the third leading cause of mortality in schizophrenia patients, which is also known as the gastrointestinal diseases (Saha et al., 2007). Also, gastrointestinal diseases are common in BPs, which can

be related to the gut microbial profile (Flowers et al., 2020). Along with the intensity and frequency of gastrointestinal symptoms, depression and anxiety symptoms increase in humans (Smith and Wissel, 2019).

Recent studies have shown that the gut-brain axis establishes a bidirectional relationship between the gastrointestinal microbiota and the brain and significantly affects the brain function and host behaviors (Collins et al., 2012; Mangiola et al., 2016; Kang et al., 2017; Knuesel and Mohajeri, 2021; Góralczyk-Bińkowska et al., 2022). Nevertheless, the exact mechanism of the effect of gastrointestinal microorganisms on the brain function and mental disorders, such as BD, is not fully understood, although it seems to involve the vagus nerve, hormones, immune system, tryptophan metabolism, and microbial metabolites, such as short-chain fatty acids (SCFAs) (Round and Mazmanian, 2009; Cryan and Dinan, 2012; Kamada et al., 2013; Dinan and Cryan, 2015; Góralczyk-Bińkowska et al., 2022). For instance, 90-95% of serotonin in the body is produced by the gut bacteria (Terry and Margolis, 2017; Strandwitz, 2018). Serotonin, as a neurotransmitter mediating happiness and well-being, has significant effects on mental disorders, especially BD. This hormone is known to decrease in the depressive phase, but is controversial in the manic phase (Mahmood and Silverstone, 2001). Evidence suggests that some *Proteobacteria*, *Lactobacillus* and *Streptococcus* species are serotonin-producing bacteria (Galland, 2014; Clark and Mach, 2016; Mazzoli and Pessione, 2016; Kaur et al., 2019).

SCFAs are metabolites produced by bacteria, which play a significant positive role in intestinal inflammation and human health. The importance of these metabolites has been confirmed in BPs (Silva et al., 2020; McGuinness et al., 2022). The phyla including *Proteobacteria*, *Actinobacteria*, *Bacteroidetes*, *Verrucomicrobia* and *Firmicutes*, genera including *Bifidobacterium*, *Clostridium*, *Dialister*, *Lactobacillus*, *Ruminococcus*, and *Streptococcus*, and species including *Akkermansia muciniphila*, *Coprococcus comes*, and *Faecalibacterium prausnitzii* have been shown to produce SCFAs, which can be exchanged with the host human blood (Ríos-Covián et al., 2016; Markowiak-Kopeć and Śliżewska, 2020; Akhtar et al., 2022; Houtman et al., 2022).

Dopamine, a neurotransmitter, plays a pivotal role in regulating mood, motivation, reward, and pleasure (Bromberg-Martin et al., 2010). In bipolar disorder, there is evidence of anomalous dopamine activity in the brain that potentially exacerbates the symptoms of the disorder (Ashok et al., 2017). Some gut bacteria can affect dopamine metabolism and function, including *Lactobacillus*, *Bifidobacterium*, *Ruminococcus*, *Clostridium*, and *Enterococcus faecalis* (González-Arancibia et al., 2019; Hamamah et al., 2022).

Additionally, some gut microbiota bacteria, including *Enterococcus faecalis*, *proteobacteria*, *Bifidobacterium*, *Streptococcus*, and *Lactobacillus*, are capable of producing gamma-aminobutyric acid (GABA), as a major inhibitory neurotransmitter which plays a key role against anxiety and depressive disorders in mammals (Dhakal et al., 2012; Dagorn et al., 2013; Duranti et al., 2020). Besides, the *Firmicutes/Bacteroidetes* (F/B) ratio plays a vital role in intestinal homeostasis, as it is directly related to the level of health, and its disruption leads to dysbiosis (Mariat et al., 2009; Magne et al., 2020; Stojanov et al., 2020).

This study aimed to measure and compare the abundance of 10 genera/species and five phyla bacteria in the fecal samples of BPs versus healthy controls (HCs) who had no history of mental disorders. Regarding the ever-increasing information about the relationship between the brain and the gut microbiota, novel studies are underway to identify the pathways of this interaction; such information can help us discover new methods of diagnosis and treatment for BD. In line with these efforts, it seems essential to find a specific bacterial biomarker for diagnostic purposes.

## 2 Methods

### 2.1 Study population

All participants in this study were selected from Roozbeh Psychiatric Hospital and the Psychosomatic Ward of Imam Khomeini Hospital (Tehran, Iran). They first completed an informed consent form and then, a prepared questionnaire. Initially, 54 people with presumed symptoms of bipolar disorders were evaluated. Among them, 30 people were recognized as BPs and participated in sample collection. To provide equal number of healthy individuals as controls, 39 apparent healthy people contributed to answering questionnaire out of which 30 people considered as HCs and donated the required samples. Therefore, a total of 60 BP and HC people who met the inclusion criteria were examined and the rest were excluded. The inclusion criteria were as follows: age 18–65 years old, BMI 18–35 kg/m<sup>2</sup>, no history of bowel or gastric surgery or history of specific diseases, absence of alcohol or antibiotic use in the past three months, absence of acute infectious diseases, absence of regular consumption of prebiotics or probiotics, not current pregnancy or breastfeeding, and no adherence to special diets and Patients without intellectual disability. The BP group included individuals with symptoms of BD, confirmed by two psychologists according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), regardless of the disorder phase, whereas the HC group included the volunteer personnel of the abovementioned hospitals, who were confirmed to be healthy by the same psychologist. It is worth mentioning that many people with bipolar symptoms refused contribution to our study often due to their special mental situations. The patients were not requested to provide an explanation for their decision to decline participation in this study. Nevertheless, a few individuals voluntarily expressed their pessimism or concerns regarding its safety. This was one of the main reasons that limited our samples sizes. The present study was approved by the Iran National Committee for Ethics in Biomedical Research with ethics code IR.IAU.TNB.REC.1400.119. Informed consent was obtained from all participants before enrollment in the study.

### 2.2 Blood of clinical characteristics

Blood samples were collected from all participants included in this study in morning concurrent with stool sample. A volume of 10 milliliters of blood was procured from each person and expeditiously transferred to the Pasteur diagnostic laboratory for analyzing the blood parameters including FT3, FT4, TSH, 25

hydroxy vitamin D3, Cholesterol, Triglyceride, Na, K, FBS, Urea, Creatinine, AST, ALT, Phosphorus, Calcium. The parameters were measured using standard laboratory methods. FT3, FT4, TSH and D3 levels were quantified through immunoassays, employing enzyme-linked immunosorbent assays (ELISA). Cholesterol and Triglyceride levels were measured by enzymatic colorimetric. Na and K were determined using ion-selective electrode (ISE). FBS was evaluated via the glucose oxidase method. Urea and Creatinine were quantified using colorimetric assays based on urease and Jaffe reaction, respectively. AST and ALT were measured through kinetic assays. Phosphorus and Calcium levels were determined using colorimetry.

Mean values from the BP and HC groups were compared using Student's T-test to survey any probable clinical characteristic- or health-related differences between the two groups.

The mean values of clinical characteristics obtained from the two groups are shown in Table 1.

\*Data are shown as means values  $\pm$  sd.  $P_{\text{value}} < 0.05$  considered as significantly different.

Abbreviations: BMI: Body Mass index; FT3: Free Triiodothyronine; FT4: Free Thyroxine; TSH: Thyroid-Stimulating Hormone; FBS: Fasting Blood Sugar; AST: Aspartate Transaminase; ALT: Alanine Transaminase.

### 2.3 Fecal sample collection and DNA extraction

Fecal samples were collected from each individual, placed in a sterile stool collection cup, and immediately transferred to laboratory on ice; they were stored at -80°C for further assessments. About 2 g of each fecal sample was used for DNA extraction with a QIAamp Power Fecal Pro DNA Kit (Germany) according to the manufacturer's instructions. The concentration and purity of extracted DNA were determined by a NanoDrop<sup>TM</sup> spectrophotometer (Thermo Scientific, USA), while the quality of DNA was examined by 1% agarose gel electrophoresis.

### 2.4 Real-time quantitative polymerase chain reaction assay

According to various databases (<https://hmdb.ca/>, <https://microbiomedb.org/>, and <https://microbiomology.org/>) and numerous studies in the literature on microbiota and psychological disorders, five phyla which might contribute to BD, including *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and *Verrucomicrobia*, alongside ten bacterial genera/species, including *Akkermansia muciniphila*, *Bifidobacterium*, *Clostridium* cluster IV, *Coprococcus comes*, *Dialister*, *Enterococcus faecalis*, *Faecalibacterium prausnitzii*, *Lactobacillus*, *Ruminococcus*, and *Streptococcus* were evaluated (Serpa et al., 2010; Pessione, 2012; Galland, 2014; Louis et al., 2014; Reichardt et al., 2014; Vital et al., 2014; Clark and Mach, 2016; Koh et al., 2016; Mazzoli and Pessione, 2016; Hu et al., 2019; Kaur et al., 2019; Lai et al., 2021; Lucidi et al., 2021; McGuinness et al., 2022). qPCR was used to assess the abundance of each bacterium in the stool samples.

Specific primers based on 16s rRNA were designed for each bacterium, as listed in Table 2. The universal primer sequences were as follows: forward primer, TCCTACGGGAGGCAGCAGT; and reverse primer, GGACTACCAGGGTATCTAATCCTGTT (Qian et al., 2018).

The qPCR reaction mixture was prepared using 10  $\mu$ L of 2X SYBR Green PCR Mix (Yekta Tajhiz Azma, Iran), 1  $\mu$ L of forward primer, 1  $\mu$ L of reverse primer (Table 2), 2  $\mu$ L of sample DNA, and 6  $\mu$ L of sterile deionized water. A Roche LightCycler 480 System (Switzerland) was also used to assess the DNA concentration of different bacterial populations in the samples.

Universal primer replication was carried out to confirm the DNA and presence of bacteria and also to confirm the steps taken so far. The concentration of target bacteria was calibrated using serial dilutions of *Escherichia coli* as a standard bacterium. Next, the dsDNA copy number of each bacterium was calculated by normalizing the bacterial concentration based on the genome size. Finally, the fold change of each bacterial population was calculated in BPs relative to HCs, based on the dsDNA copy numbers. Also, the F/B ratio was calculated in both groups as an index of health status.

## 2.5 Metabolic network and correlation analysis

We conducted a literature review and summarized the bacteria that were assessed in this study for their involvement in the production of SCFA, GABA, dopamine and serotonin. These substances are commonly associated with BD. Subsequently, we constructed a hypothetical metabolic network of the bacteria. Also, we conducted a correlation analysis to demonstrate the relationship between the population of different bacteria within the experimental groups.

## 2.6 Statistical analyses

The collected data were analyzed using SPSS Version 26. T-test and independent-samples Mann-Whitney U test were used to compare the mean values of different groups. The relationships between the population of the bacteria were measured using Pearson correlation coefficient. A *P*-value less than 0.05 was considered as statistically significant.

TABLE 1 Baseline demography and clinical characteristics.

	BP	HC	<i>P</i> <sub>value</sub>	Normal range
Parameters	30	30	0.611	
Gender	13 male/17 female	15 male/15 female		
Age(years)*	38.5 $\pm$ 11.68	39 $\pm$ 9.47	0.903	
Weight (kg)	73.46 $\pm$ 12.95	65.9 $\pm$ 8.12	0.252	
Height (m)	1.67 $\pm$ 0.10	1.68 $\pm$ 8.43	0.683	
BMI (kg/m <sup>2</sup> )	26.33 $\pm$ 4.29	22.11 $\pm$ 1.36	0.103	18.5-24.9
FT3 (pg/mL)	3.21 $\pm$ 0.35	4.98 $\pm$ 0.55	<0.001	2.3 - 4.2
FT4 (pg/mL)	1.317 $\pm$ 0.33	1.07 $\pm$ 0.29	0.087	0.7- 1.9
TSH (mIU/mL)	2.3 $\pm$ 1.46	2.36 $\pm$ 1.06	0.914	0.5- 5.0
25 hydroxy vitamin D3 (ng/mL)	38.34 $\pm$ 10.19	45.66 $\pm$ 21.40	0.470	20-40
Cholesterol (mg/dL)	188.75 $\pm$ 49.29	150.33 $\pm$ 34.09	0.023	Less than 200
Triglyceride (mg/dL)	150.37 $\pm$ 54.40	115.37 $\pm$ 58.28	0.170	Less than 150
Na (mEq/L)	139.5 $\pm$ 2.39	140.43 $\pm$ 1.80	0.267	135-145
K (mEq/L)	4.25 $\pm$ 0.32	4.21 $\pm$ 0.33	0.757	3.6-5.2
FBS (mg/dL)	90.37 $\pm$ 14.00	90.5 $\pm$ 9.36	0.978	60-110
Urea (mg/dL)	49.87 $\pm$ 38.18	26.67 $\pm$ 7.63	0.030	15-50
Creatinine (mg/dL)	1.48 $\pm$ 1.47	0.95 $\pm$ 0.14	0.118	0.7-1.4
AST (U/L)	24 $\pm$ 5.25	22.11 $\pm$ 8.40	0.614	8-33
ALT (U/L)	25.67 $\pm$ 20.84	21.81 $\pm$ 7.49	0.519	4-36
Phosphorus (mg/dL)	8.77 $\pm$ 0.98	9.27 $\pm$ 0.43	0.396	2.5-5
Calcium (mg/dL)	8.771 $\pm$ 0.56	9.266 $\pm$ 0.39	0.014	8.6-10.3

BP, Bipolar patient; HC, Healthy controls.

## 3 Results

### 3.1 Gut microbiota

As shown in Table 1, all parameters assessed in the BP and HC groups were in the normal ranges ( $P>0.1$ ). Also, all the parameters except FT3 were not significantly different between the groups. The

level of free triiodothyronine (FT3) was significantly lower in BPs compared to HCs ( $P<0.001$ ).

Additionally, the abundance of all bacteria assessed in this study significantly changed in BPs compared to HCs (Table 3).

The phylum *Actinobacteria* with a fold change of 200 and the genus *Lactobacillus* with a fold change of 45,700 showed the greatest changes, while the phylum *Bacteroidetes* with a fold change of

TABLE 2 List of primer sequences used for qPCR.

Microorganism		Primer sequence (5'–3')	Refs
<b>Part A: phylum</b>			
<i>Actinobacteria</i>	F	CGCGGCTATCAGCTTGTG	(Bredholt et al., 2008)
	R	CCGTACTCCCCAGGCGGG	
<i>Bacteroidetes</i>	F	GGAACATGTGGTTTAATTCGATGAT	(Layton et al., 2006)
	R	AGCTGACGACAACCATGCAG	
<i>Firmicutes</i>	F	GGAGYATGTGGTTTAATTCGAAGCA	(Yi et al., 2019)
	R	AGCTGACGACAACCARGCAC	
<i>Verrucomicrobia</i>	F	GAATTCTCGGTGTAGCA	(Hermann-Bank et al., 2013)
	R	GGCATTGTAGTACGTGTGCA	
<i>Proteobacteria</i>		CATGACGTTACCCGAGAAGAAG	(Murri et al., 2013)
		CTCTACGAGACTCAAGCTTGC	
<b>Part B: Genus, species</b>			
<i>Akkermansia muciniphila</i>	F	CAGCACGTGAAGGTGGGGAC	(Schneeberger et al., 2015)
	R	CCTTGCGGTTGGCTTCAGAT	
<i>Bifidobacterium spp</i>	F	TCGCGTCYGGTGTGAAAG	(Schneeberger et al., 2015)
	R	CCACATCCAGCRTCCAC	
<i>Coprococcus comes</i>	F	GTGACCGCGTGAATGACG	(Kurakawa et al., 2016)
	R	CAGAGTGCCCATCCGAATTG	
<i>Dialister spp</i>	F	CGGAATTATTGGGCGTAAAG	(Sun et al., 2017)
	R	CTTTCCTCTCCGATACTCCA	
<i>Enterococcus faecalis</i>	F	ACGTGCTTCCATCAACGCT	(Arabestani et al., 2017)
	R	ACTGCTGTATGTTGTCTCCGA	
<i>Faecalibacterium prausnitzii</i>	F	GGAGGAAGAAGGTCTTCGG	(Fitzgerald et al., 2018)
	R	AATCCGCCTACCTCTGCACT	
<i>Lactobacillus spp</i>	F	AGCAGTAGGGAATCTTCCA	(Alioua et al., 2016)
	R	ATTYCACCGCTACACATG	
<i>Ruminococcus spp</i>	F	GAGTGAAGTAGAGGTAAGCGGAATTC	(Weimer et al., 2008)
	R	GCCGTACTCCCCAGGTGG	
<i>Streptococcus spp</i>	F	AGTCGGTGAGGTAACCCTAAG	(Hall-Stoodley et al., 2006)
	R	AGGAGGTGATCCAACCGCA	
<b>Part C: Clostridium cluster IV</b>			
<i>Clostridium IV</i>	F	ACAATAAGTAATCCACCTGG	(Hermann-Bank et al., 2013)
	R	CTTCTCCGTTTGTCAA	



TABLE 3 Fold change differences in the gut bacteria of BDs compared to HCs.

	BD	HC	Fold change	(P <sub>value</sub> )
<i>Actinobacteria</i>	2.21E-03	1.11E-05	2.00E+02	< 0.001
<i>Akkermansia muciniphila</i>	34093.05	4.23E+12	8.06E-09	< 0.001
<i>Bacteroidetes</i>	83.32341	3.58E+10	2.33E-09	< 0.001
<i>Bifidobacterium spp</i>	1492871	1.05E+13	1.42E-07	< 0.001
<i>Clostridium iv</i>	7.612204	0.086185	8.83E+01	< 0.001
<i>Coprococcus comes</i>	1.17E+05	1.29E+04	9.11E+00	< 0.001
<i>Dialister spp</i>	7031724	5.03E+09	1.40E-03	< 0.001
<i>Enterococcus faecalis</i>	1.60E+03	8.60E+01	1.86E+01	< 0.001
<i>Faecalibacterium prausnitzii</i>	8.11E+06	6.49E+11	1.25E-05	< 0.001
<i>Firmicutes</i>	400.1563	2.55E+08	1.57E-06	< 0.001
<i>Lactobacillus spp</i>	48941432	1071.715	4.57E+04	< 0.001
<i>Proteobacteria</i>	548.176	391.1138	1.40E+00	< 0.001
<i>Ruminococcus spp</i>	1.00E+08	1.16E+13	8.66E-06	< 0.001
<i>Streptococcus spp</i>	1.29E+07	2.73E+09	4.73E-03	< 0.001

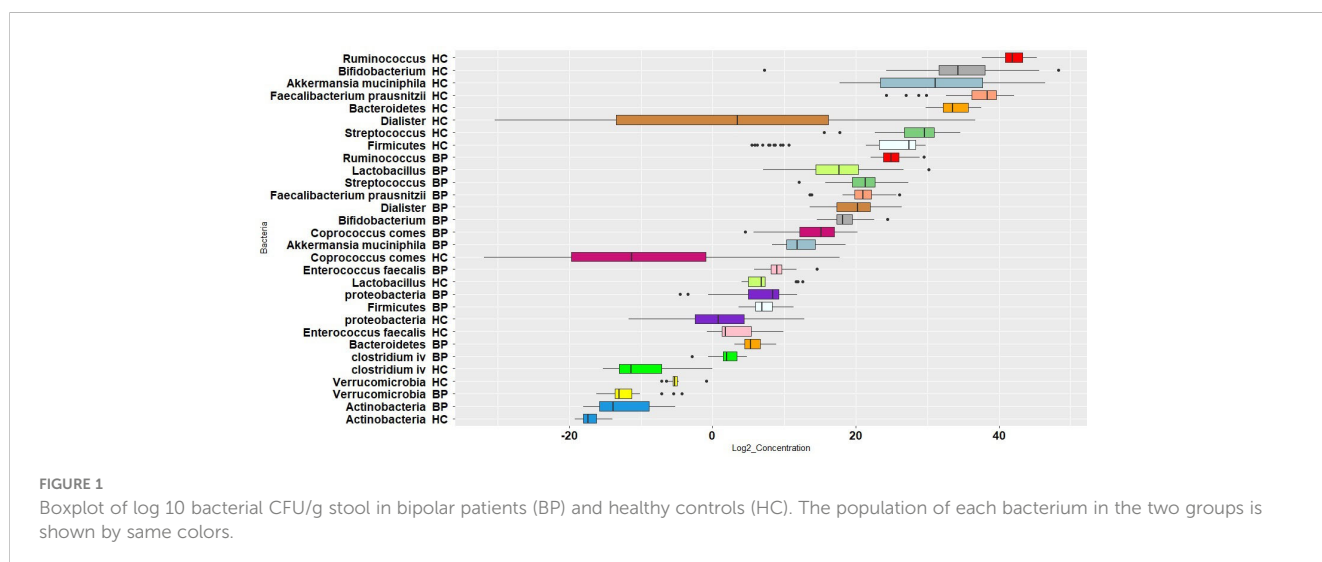
BD, Bipolar disorder; HCs, Healthy controls.

0.0000000233 and *Akkermansia muciniphila* with a fold change of 0.0000000806 showed the least changes in BPs compared to HCs. The abundance of genera/species, including *Akkermansia muciniphila*, *Bifidobacterium*, *Faecalibacterium prausnitzii*, *Dialister*, *Streptococcus*, and *Ruminococcus*, as well as phyla including *Bacteroidetes*, *Firmicutes*, and *Verrucomicrobia*, was lower in BPs, while the abundance of *Clostridium* cluster IV, *Lactobacillus*, *Coprococcus comes* and *Enterococcus faecalis* species, and the phylum *Actinobacteria* and *Proteobacteria* was higher in BPs compared to HCs.

Figure 1 presents log<sub>10</sub> CFU/g of bacteria in BP and HC groups. *Clostridium* cluster IV and the phylum *Actinobacteria* showed the lowest abundance, while the genus *Ruminococcus* and

the phylum *proteobacteria* showed the highest abundance in BPs. In HCs, *Clostridium* cluster IV and the phylum *Actinobacteria* had the lowest abundance, whereas the genus *Ruminococcus* and the phylum *Bacteroidetes* were the largest populations. The concentration distribution of each bacterium in the two groups is shown in Figure 2 for a simpler comparison.

Figure 3 summarizes the population percentage of different bacterial populations in BP and HC groups. The phylum *Proteobacteria* accounted for 53% of bacteria in BPs, while in HCs, only 1% of bacteria were in the phylum *Firmicutes*; the phylum *Bacteroidetes* comprised 99% of the assessed bacteria in HCs. On the other hand, the genus *Ruminococcus* was the predominant population in BP and HC groups (56% and 43%, respectively).



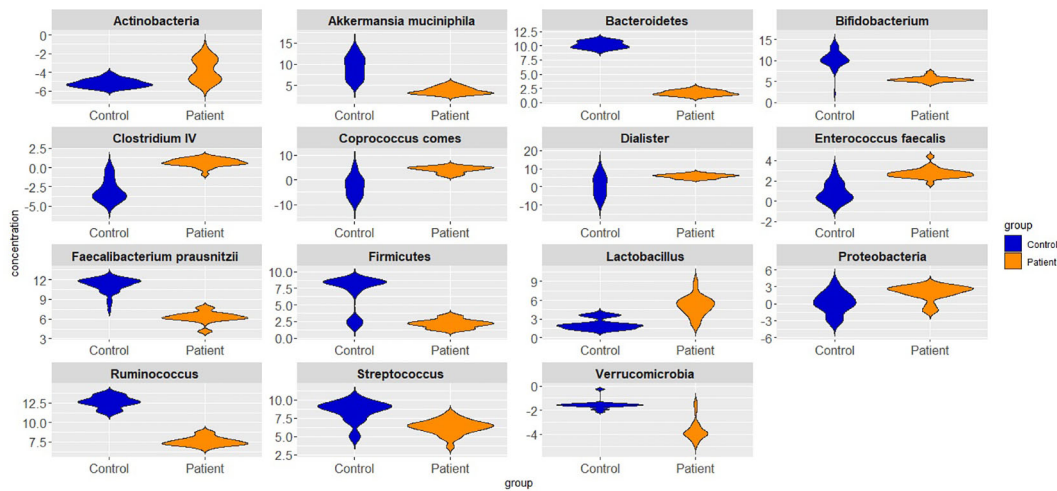


FIGURE 2 Violin plots showing different bacterial abundances in bipolar patients and healthy controls.

The mean concentrations of *Bacteroidetes* and *Firmicutes*, along with the F/B ratio, are presented in Table 4. The mean of F/B ratios was significantly higher in BPs compared to HCs.

The metabolic network of the assessed bacteria is shown in Figure 4. Fourteen out of fifteen bacteria were SCFA-producing

bacteria. Five out of these Fourteen bacterial populations could also produce other substances concomitantly with SCFAs, which were involved in mental function. Dopamine, GABA and serotonin with five, four and three edges, respectively, are other substances that seem to be the main intermediates in this network (Figure 4).

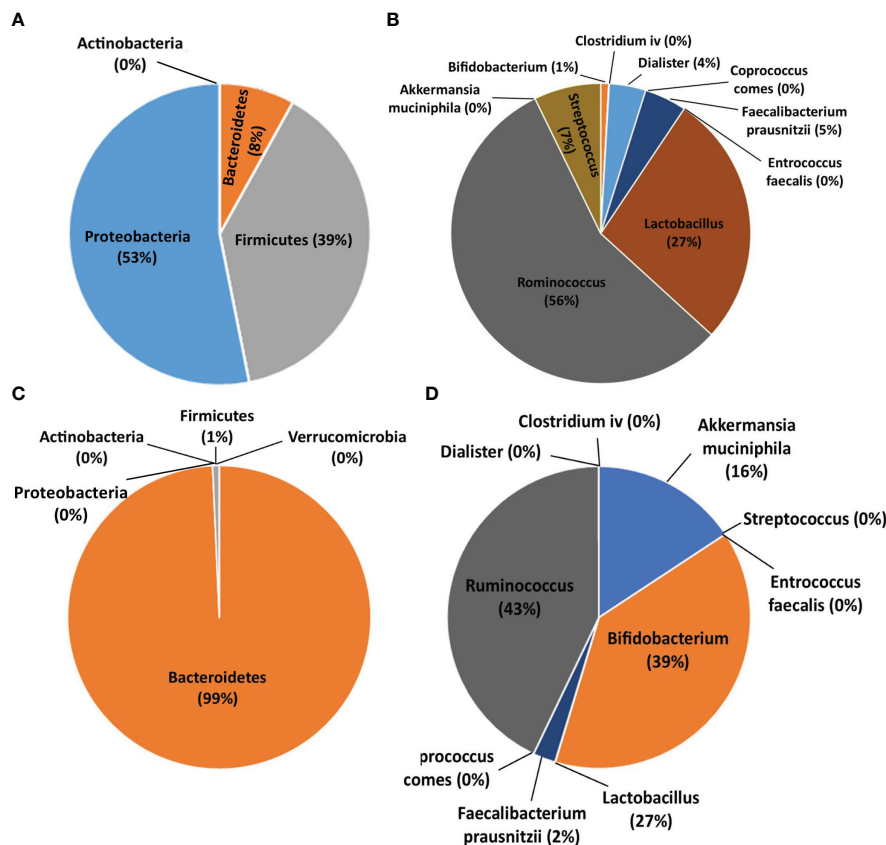


FIGURE 3 Pie charts showing the population percentage of each bacterium in bipolar patients (BPs) and healthy controls (HCs). (A) Abundance of bacteria at the phylum level in BPs. (B) Abundance of bacteria at the genus and species level in BPs. (C) Abundance of bacteria at the phylum level in HCs. (D) Abundance of bacteria at the genus and species level in HCs.

TABLE 4 Firmicutes/Bacteroidetes (F/B) ratio.

Species	Group	(Mean $\pm$ SD)	F	(P value)
F/B	BPs	5.841 $\pm$ 6.239	44.05	<0.001
	HCs	0.018 $\pm$ 0.033		

BPs, Bipolar patients; HCs, Healthy controls; F/B, Firmicutes/Bacteroidetes.

### 3.2 Population correlations

The relationships between bacterial populations in BPs revealed positive significant (adjusted  $P < 0.05$ ) correlations among several species, including *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Dialister*, *Akkermansia muciniphila*, *Bacteroidetes*, *Ruminococcus*, *Faecalibacterium prausnitzii* and *Ruminococcus* (Figure 5). *Faecalibacterium prausnitzii* and *Ruminococcus* exhibited positive significant correlations with *Firmicutes* as well. *Firmicutes* showed similar correlation with *Streptococcus* and *Lactobacillus*. Additionally, *Verrucomicrobia* demonstrated a positive correlation with *Actinobacteria* (Figure 5).

In HCs, positive, and significant (adjusted  $P < 0.05$ ) correlation was observed between the population of *Proteobacteria*, *Verrucomicrobia*, and *Akkermansia muciniphila*. Furthermore, positive and significant correlations were found between the populations of *Coprococcus comes*, *Actinobacteria* and *Dialister*. Additionally, *Firmicutes* exhibited a positive correlation with *Enterococcus Faecalis* (Figure 6).

## 4 Discussion

Dysbiosis in the gut microbiota has been linked to the development of some neuropsychiatric disorders. In the present

study, we provided the first evidence for the altered gut microbiota in BPs in the Iranian population. For the selection of samples, caution was taken not to include patients who used certain drugs, had a disease, or had other factors that could affect the bacterial flora. The patients were all hospitalized, and their disorder was confirmed based on an interview and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) results. Bacteria with a more pronounced impact and change in psychiatric patients were carefully selected for this study.

Our results showed that the genus/species *Clostridium IV*, *Enterococcus faecalis*, *Lactobacillus* and *Coprococcus comes*, phylum *Actinobacteria* and *Proteobacteria* increased and the genus/species, *Bifidobacterium*, *Dialister*, *Faecalibacterium prausnitzii*, *Streptococcus*, *Ruminococcus*, *Akkermansia muciniphila*, phylum *Verrucomicrobia*, *Bacteroidetes*, and *Firmicutes* decreased in the stool of BPs compared to HCs showing distinct and altered gut microbiota in BPs.

The gut microbiota produce neurotransmitter such as GABA, serotonin and dopamine which can be released into the blood stream and potentially modulate mental health via the gut-brain axis.

The neurotransmitters GABA, serotonin, and dopamine, known for their crucial roles in the nervous system, have sparked interest in their potential effects on the immune system (Herr et al., 2017; Matt and Gaskill, 2020; Bhandage and Barragan, 2021; Oshaghi et al., 2023). Serotonin and dopamine receptors found on immune cells imply modulatory effects on them (Herr et al., 2017; Channer et al., 2023). Additionally, certain antidepressant medications regulating neurotransmitters exhibit immunomodulatory properties (Nestler et al., 2002). Nevertheless, the immune system's core regulation primarily relies on cytokines and immune-specific factors. Serotonin-immune cell interaction has been link to neurobehavioral disorders by modulational inflammatory cytokine acting withing the brain (Baganz and Blakely, 2013). Also, dopamine signaling can modulate cytokine secretion and immune function and provide for immunological behavior-switching (Hodo et al., 2020). The above evidences may lead us to extrapolate that the immune system may play a mediatory role in the gut-brain-axis.

Serotonin, commonly referred to as the "hormone of happiness," is implicated in the etiology of depression, sadness, apathy, and anxiety when deficient (Góralczyk-Bińkowska et al., 2022). The present results revealed that the abundance of *Streptococcus* and *Lactobacillus* species, as serotonin-producing bacteria, decreased and increased, respectively, in BPs compared to HCs. Previous studies have reported an increase in both bacterial populations in BPs (Lai et al., 2021; Lucidi et al., 2021; McGuinness et al., 2022). Decreased serotonin in the depressive phase of bipolar disorder may be associated with decreased *Streptococcus*



FIGURE 4  
Metabolic network drawn based on the metabolites produced by the assessed bacteria using Cytoscape. Yellow and blue nodes demonstrate the bacteria and their metabolites, respectively. Short-chain fatty acid (SCFA), shown by red node, seems to function as the central metabolite in this network produced by various bacteria.



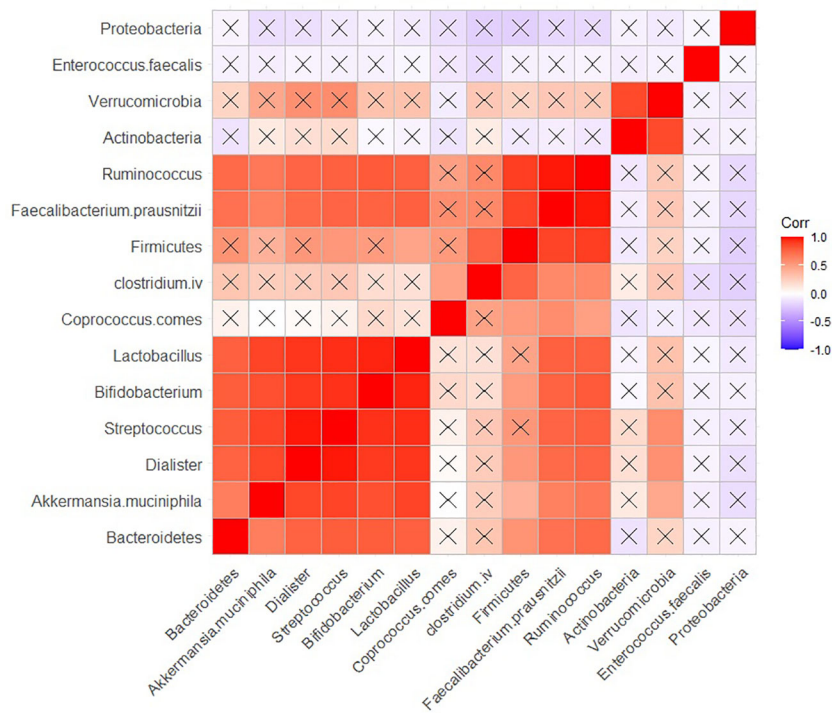


FIGURE 5 Correlation between the population of different bacteria in BP group. Raw and adjusted probability values are reported below and above the diagonal elements, respectively.

(Mahmood and Silverstone, 2001). Additionally, a study has reported a positive correlation between serotonin and *Proteobacteria* (Barandouzi et al., 2022). In our study, *Proteobacteria* was higher in BPs than HCs. Whether *Proteobacteria* is also associated with the level of serotonin in bipolar people needs to be elucidated in the future.

Dopamine is another neurotransmitter that potentially plays a role in individuals with bipolar disorder and its associated dysfunctions (Ashok et al., 2017). Moreover, previous studies have suggested that certain gut bacteria can affect dopamine metabolism and function, including *Lactobacillus*, *Bifidobacterium*, *Ruminococcus*, *Clostridium*, and *Enterococcus faecalis* (González-Arancibia et al., 2019; Hamamah et al., 2022). In this study, we investigated the abundances of these bacteria and found a decrease in *Ruminococcus*, and *Bifidobacterium* an increase in *Lactobacillus*, *Clostridium IV*, and *Enterococcus faecalis* indicating that alterations in these gut bacteria may be linked to bipolar disorder in affected individuals.

GABA serves as the principal inhibitory neurotransmitter within the brain, and is capable of being synthesized by gut bacteria. Geuze et al. showed the association of GABA and mental health in patients with depression and anxiety (Geuze et al., 2008). Regarding GABA neurotransmitter-producing bacteria, our findings showed a decrease in *Bifidobacterium*, and *Streptococcus* species and an increase in the abundance of *Lactobacillus*, *Proteobacteria* and *Enterococcus faecalis*, which might cause an imbalance in the abundance of GABA-producing bacteria in BPs and impair the normal function of the gut-brain axis. Previous studies have reported an increase in *Lactobacillus*,

*Bifidobacterium*, *Proteobacteria* and, *Streptococcus* bacteria in BPs (Hu et al., 2019; Lai et al., 2020; Lai et al., 2021; Lucidi et al., 2021; McGuinness et al., 2022).

In the current study, the proportion of SCFA-producing bacteria, including *Bifidobacterium*, *Firmicutes*, *Streptococcus*, *Akkermansia muciniphila*, *Bacteroidetes*, *Dialister*, *Ruminococcus*, and *Faecalibacterium prausnitzii*, was lower abundance and *Proteobacteria*, *Actinobacteria*, *Clostridium IV* and *Lactobacillus* were higher abundance in BPs, which is consistent with previous research (Hu et al., 2019; Lu et al., 2019; Parada Venegas et al., 2019; Guo et al., 2020; Lai et al., 2020; Markowiak-Kopeć and Śliżewska, 2020; Lucidi et al., 2021; Li Z. et al., 2022). In general, the finding suggests that individuals with bipolar disorder exhibit a decrease in the abundance of bacteria that produce SCFA, which may imply their potential advantageous impact (Knuesel and Mohajeri, 2021). Our study is probably the first report showing a decrease in the abundance of *Coprococcus comes* in BPs compared to HCs. In contrary to the current findings, the abundances of *Bifidobacterium*, *Streptococcus*, *Verrucomicrobia*, and *Bacteroidetes* populations were higher in bipolar people in previous studies (Dong et al., 2021; Lucidi et al., 2021; McGuinness et al., 2022). These bacteria are involved in the production of SCFAs and they may affect the human body and mental health and reduce intestinal inflammation, which is very common in BPs. BPs have had lower levels of SCFA compared to HCs (Dai et al., 2022). This could be caused by reduced population of these bacteria in BPs (Rivière et al., 2016; Dalile et al., 2019b; Lu et al., 2019; Parada Venegas et al., 2019; Markowiak-Kopeć and Śliżewska, 2020; Müller et al., 2021).

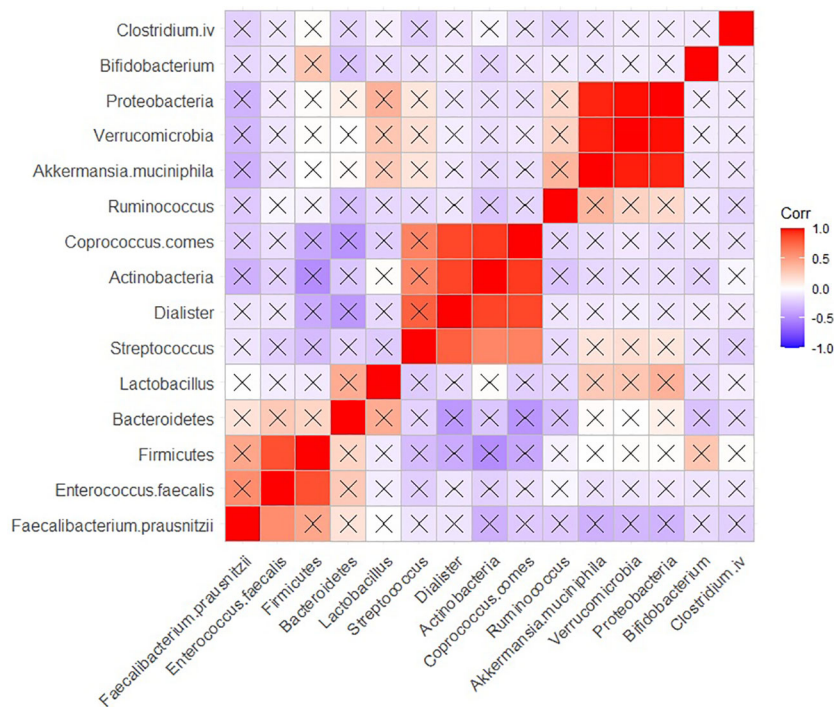


FIGURE 6 Correlation heatmap of the population of the bacteria in HC group. Raw and adjusted probability values are reported below and above the diagonal elements, respectively.

Reduction in the production of SCFA and the bacteria responsible for their synthesis could provide evidence for the correlation between these bacteria and bipolar disorder and would demonstrate a link between gut bacteria and mental health. SCFA produced from intestinal microbiota, in addition to the local effect in digestion, by binding to brain cell receptors, can affect gut-brain signaling (Dalile et al., 2019a). Moreover, short-chain fatty acids (SCFAs) induce neuroendocrine cells to convert amino acids into serotonin (Smith and Wissel, 2019). Therefore, SCFAs could also potentially affect mental health through the action of serotonin.

Similar to the result of the previous study, *Ruminococcus* decreased in bipolar people which may reinforce the idea of impaired energy metabolism in BPs (Hu et al., 2019).

Based on our data, *Verrucomicrobia* decreased in BPs. Dong et al. (Dong et al., 2021) reported an increase in the population of *Verrucomicrobia* in patients with general anxiety disorder, whereas Hemmings et al. (Hemmings et al., 2017) showed a reduction in this population in patients with posttraumatic stress disorder. This could be related to differences between mental illnesses.

In the current study, a relationship was observed between bacteria producing small molecule metabolites. This relationship was pronounced for SCFAs, GABA, dopamine and serotonin. These bacteria with overlapping metabolites could be potentially involved in cognitive impairments in BD. Therefore, our results suggest that imbalances in GABA and SCFAs might be potential metabolites that play a role in malfunctioning of gut-brain axis in bipolar patients.

Regarding the clinical characteristics in the current study, all the assessed blood parameters were in the normal physiological ranges

in the both groups, showing the normal body condition of all participants. In addition, the parameters were not significantly different between the groups suggesting that these parameters have not affected the gut-brain axis. However, the level of FT3 was rather controversial and was significantly lower in BPs than HCs ( $P < 0.001$ ). Long-term lithium treatment has been shown to decrease FT3 (Kraszewska et al., 2019). As lithium consumption is a routine treatment for bipolar patients, it may have impacted the blood concentration of FT3 in the BPs.

In the present study, significant differences were found in the microbiota of BP and HC groups.

*Firmicutes* are gram-positive bacteria that can play an essential role in both mental and physical health due to their effects on the production of SCFAs. *Bacteroidetes*, on the other hand, are gram-negative bacteria that can induce cytokine synthesis and strengthen immune reactions through their lipopolysaccharides and flagellin components (Stojanov et al., 2020). Several studies have shown that the F/B ratio is related to health status and plays a significant role in maintaining intestinal homeostasis. Deviations from the F/B ratio seen in healthy controls have been correlated with various diseases (Stojanov et al., 2020; An et al., 2023), and in increases in this ratio have been documented in studies on conditions such as Autism spectrum, irritable bowel syndrome, and obesity (Bahr et al., 2015; Lach et al., 2018; Huang et al., 2019; Stojanov et al., 2020). In our study, we found that the F/B ratio was higher in BPs compared to HCs, suggesting that this parameter could also be considered as a candidate marker for BP.

We conducted a series of correlation studies between the populations of bacteria assessed in this study within the BP and

HC groups. No significant negative correlation was observed between the bacterial populations, indicating the absence of a competitive relationship among these bacteria. However, we did find a significant positive correlation between certain bacteria, suggesting a prevalent commensalism and mutualism relationship among them.

In BPs, *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Dialister*, *Akeermansia muciniphila*, *Bacteroidetes*, *Ruminococcus*, and *Faecalibacterium prausnitzii* showed a strong positive correlation with each other. Similarly, *Verrucomicrobia* and *Actinobacteria*, as well as *Firmicutes*, *Faecalibacterium prausnitzii* and *Ruminococcus* exhibited positive significant correlations with each other. All aforementioned bacteria are SCFA-producing bacteria, which suggests that short-chain fatty acids (SCFAs) may serve as intermediary substances influencing the interactions and population dynamics of these bacteria in BPs.

Furthermore, both *Lactobacillus* and *Bifidobacterium* are among the bacteria that produce GABA and dopamine. This may indicate the presence of potential intermediates that could link these two species together. Future studies should explore these relationships more comprehensively.

In HCs, we found significant positive correlations between *Coprococcus comes*, *Actinobacteria* and *Dialister*. Additionally, a positive correlation was observed between *Proteobacteria*, *Verrucomicrobia*, and *Akkermansia muciniphila*. Short chain fatty acids, which are commonly produced by these bacteria, may serve as candidate intermediates mediating their interactions as well. Moreover, we identified a positive and significant correlation between *Firmicutes* and *Enterococcus faecalis*. In the literature, we could not find any common substances associated with mental functions produced by these bacteria, leaving us unable to speculate about potential intermediates connecting these two bacterial species.

Based on the correlation results, it seems that there is a significant shift in the relationship between bacterial populations in individuals with bipolar disorder compared to healthy controls. This suggests that the level of interactions between bacterial populations increases in BPs due to the higher number of bacteria involved in these interactions. Additionally, the profile of interactions appears to differ, with changes in the species and genera that are correlated with each other. This may indicate that one way in which bipolar disorder affects or is affected by the gut-brain axis is through alterations in the interaction patterns of gut microbiota.

Currently, numerous studies focusing on depression, anxiety, autism, schizophrenia, and bipolar disorder indicate that probiotics represent an effective treatment modality for these mental disorders by enhancing gut permeability (Góralczyk-Bińkowska et al., 2022). The effects of probiotic bacteria on bipolar disorder have received limited research attention to date. Nevertheless, some studies have indicated that probiotics could potentially improve mood and cognitive function in individuals with this disorder. Specifically, probiotic supplementation has been shown to enhance mood and alleviate symptoms of anxiety and depression, as well as decrease the rate of rehospitalization (Aizawa et al., 2018; Reininghaus et al., 2018; Genedi et al., 2019). In addition, probiotics have been shown to be effective in various ways, including the production of short-

chain fatty acids, regulation of the immune system, and support of intestinal barrier integrity (Góralczyk-Bińkowska et al., 2022). Normalizing the population of gut bacteria in bipolar and making them more similar to healthy people may represent a promising treatment approach for managing bipolar disorder. Thus, utilizing the bacteria assessed in our study, perhaps as probiotics, could be considered for future studies.

Based on the present results, the abundance of beneficial bacteria such as *Bifidobacterium* and *Akkermansia muciniphila* significantly reduced in BPs compared to HCs, which indicates the significant effect of gut microbiota on BD through the gut-brain axis. The present results were mostly consistent with the results of previous research, although in some cases, different results were obtained, which could originate from racial, genetic, lifestyle, dietary, and other factors that vary from one country to another and have significant effects on the microbiota in humans.

## 5 Limitations

Our study faced several limitations that should be acknowledged. Firstly, the sample size was small, which was due to the difficulty of recruiting individuals with bipolar disorder because of their specific mental conditions and reluctance to seek medical attention. This made the sampling process lengthy and challenging. Additionally, patients had to meet certain criteria to be included in the study, such as not consuming alcohol in the past month, which was a significant limitation given the unique habits and mental conditions of these patients. We also implemented strict exclusion criteria for the dietary habits of participants in our study using a questionnaire. However, as the participants did not consume a fixed and normalized diet, this could have been a source of variation in the data.

## 6 Conclusion

There has been increasing attention paid to the impact of gut microbiota on various diseases, including mental disorders. The bidirectional relationship between the gut and brain is well-documented in numerous studies conducted across different countries. This study is the first of its kind in an Iranian population, and the results indicate that BPs have a distinct gut ecosystem and likely a malfunctioning gut-brain axis. All bacteria examined in this study showed significant differences between BPs and HCs, suggesting that these bacteria could serve as microbial markers for diagnosing bipolar patients. Normalizing their population could be targeted through probiotic or medical interventions to alleviate the signs and symptoms of BD. Our findings could prove valuable to psychologists in clinical settings, as they may gain a deeper understanding of the physiological factors involved in bipolar disorder. Additionally, these results could encourage psychologists to keep a closer eye on their patients' nutritional intake, medication usage, and gut microbiota profiling. Further research can enhance our understanding of the role of these bacterial populations in the GBA, leading to better decision-making in treating BP.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by The present study was approved by the Iran National Committee for Ethics in Biomedical Research with ethics code IR.IAU.TNB.REC.1400.119. Informed consent was obtained from all participants before enrollment in the study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

All listed authors have made significant, direct, and intellectual contributions to this work and have granted their approval for its publication.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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