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Probiotic food consumption is associated with lower severity and prevalence of depression: A nationwide cross-sectional study

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ABSTRACT

Objective: It has been suggested that probiotics have beneficial effects on a variety of health problems including immunologic diseases and metabolic disorders, however, the effects on brain function are yet to be fully studied. The aim of this study was to evaluate the association between probiotic food consumption and depression status through a cross-sectional analysis of a nationwide, large population-based data.
Methods: The study population included 26 118 individuals 19 to 64 y of age who participated in the Korean National Health and Nutrition Examination Survey (KNHANES, 2012–2016). A food frequency questionnaire was used to assess probiotic food consumption. Depression status was determined by two different methods including a Patient Health Questionnaire (PHQ-9) and self-reported clinical diagnosis.
Results: Compared with the lowest tertile of probiotic food consumption, the highest tertile had significantly lower odds in PHQ-9 depression severity (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.28–0.81; $P = 0.0065$) and self-reported clinical depression (OR, 0.59; 95% CI, 0.35–0.96; $P = 0.0129$). Although there was no significant association between probiotic food consumption and clinical depression in women (OR, 0.85; 95% CI, 0.47–1.54; $P = 0.3081$), men showed a significantly lower prevalence of clinical depression (OR, 0.24; 95% CI, 0.06–0.92; $P = 0.0256$) in the highest tertile.
Conclusions: These results suggest that probiotic food consumption might have beneficial effects on depression, particularly in men. Further studies are required to identify the mechanistic relations between probiotics and depression.

Introduction

The World Health Organization (WHO) reports mental disorders will become the leading disease in 2020 and therefore they represent a major challenge in public health [1]. Depression is one of the most common psychological disorders and >320 million people are currently diagnosed with the disorder worldwide [2]. A high prevalence of depression leads to increased socioeconomic burden; increased risk for developing several diseases including cancer, heart disease, and suicide; and decreased work productivity and overall quality of life [2]. Moreover, fully effective therapeutic strategies for the treatment of depression have yet to be developed because about one-third of patients do not respond to standard antidepressants [3]. To reduce the increasing public burden of the disorders, it will be critical to develop and implement effective health care strategies that promote mental health.

The gut microbiota, a community of bacteria colonizing the human gut, has a symbiotic and mutualistic relationship with humans [4,5]. Recent evidence suggests that the gut microbiota interacts with the host central nervous system via the gut–brain axis [6–8]. It is being actively studied that the gut microbiota has far-reaching effects on brain development, functions, and behaviors of the host, using animal models [6,9,10]. In a rodent study, young germ-free animals showed abnormal hippocampal development and risk-taking behaviors, which were normalized after bacterial colonization [11]. In addition, germ-free mice revealed altered neuronal development affecting neuroendocrine function and response to stress [12]. Moreover, several studies showed that gut microbial dysbiosis might be implicated in neuropsychiatric problems such as schizophrenia, bipolar disorder, and depression [10]. Although the evidences from human studies are limited, individuals with mental disorders, such as major depressive disorder (MDD), have distinct microbial compositions compared with

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healthy controls [13,14]. Thus, these findings support the idea that the gut microbiota might be a novel potential target for antidepressant agents.

Diet and nutrition have received increasing attention for their important roles in regulating mental health. Current evidence shows dietary patterns and specific dietary factors linked to mental illness. It is noteworthy that dietary patterns such as a traditional Western diet with higher fat and sugary products is involved in the increased risk for mental disorders such as aggression [15], anxiety, and depression [16,17]; whereas the Mediterranean dietary pattern is inversely correlated with the incidence of depression [18]. Moreover, several systematic reviews on the effect of the quality of habitual diet in mental health support the idea that manipulation of mental health problems could be achieved by nutritional interventions [19–21]. Regarding mood disorders, a tryptophan-rich diet is known to reduce stress-related mood deterioration by regulating serotonin levels [22,23]. In addition, a diet rich in ω-3 polyunsaturated fatty acids and flavonoids appears to reduce the risk for depression [24,25]. Therefore, diet and nutrition have become compelling alternatives to medications in mental illness.

Probiotics are live microorganisms that have beneficial health effects when consumed [26], and they are available in dietary supplements and foods including fermented dairy products and fermented vegetables [27]. A growing body of evidence suggests that probiotics as a part of healthy diet act as possible anxiolytic and antidepressive agents [28,29]. In preclinical studies, consumption of probiotics increased the level of critical neurotransmitter in depression such as γ-aminobutyric acid [30], serotonin and its precursor [31,32], and brain-derived neurotrophic factor [33,34]. Rodents treated with probiotics had reduced levels of proinflammatory cytokines implicated in depression with reduced anxiety and depressive-like behaviors [35–39]. In addition, probiotic supplementation in patients with MDD showed significantly reduced severity of depression in self-reported mood test [40,41]. Benton et al. reported that probiotics improved mood in individuals whose mood was poor at baseline among healthy individuals [42]. Furthermore, clinical studies in healthy individuals demonstrated that consumption of probiotics had no effects on stress or anxiety [43] but had significant effects on cognitive reactivity to sad mood and depression [44,45].

Although there are systematic reviews on the probiotics that affect depressive symptoms and anxiety [46–48] in the patient with mental illness, currently available evidences are not enough to conclusively demonstrate the effects of probiotics on mental health. These are partly due to the limitations of small sample sizes, heterogeneity of dose and strains, and the difference in duration of intervention. In addition, there are few studies that investigated the relationship between probiotic foods that people routinely consume (not as a supplement) and the status of depression. Therefore, we sought to conduct a well-controlled, large population-based study for better understanding of the regulatory roles of probiotics on depression. In the present study, we aimed to investigate the hypothesis that probiotic food consumption is negatively associated with the prevalence or severity of depression using a nationwide, large population-based database.

Methods

Data source and study population

We conducted a large population-based, cross-sectional, nationwide analysis using the Korean National Health and Nutrition Examination Survey (KNHANES V, KNHANES VI-1), 2012– 2016, conducted by the Korea Centers for Disease Control and Prevention (KCDC). The KNHANES is a national survey that assesses the health and nutritional status from a representative sample of the Korean population. This study was approved by the Institutional Review Board (IRB) of the Korea Centers for Disease Control and Prevention, and written informed consent was obtained from all participants.

There are two parts of analyses depending on the methods used for assessment of depression in this study. First, we analyzed the association between probiotic food consumption and the extent of current depressive symptoms and its severity with the participants enrolled in the KNHANES VI-1 (2016). Second, we investigated the effects of probiotic food consumption on a final diagnosis of depression made by a clinician among the individuals who participated in the KNHANES V (2012–2015).

The KNHANES is composed of three surveys: interviews assessing health, interviews assessing nutritional status, and physical examinations [49]. The surveys collect detailed information including demographic and social status, health behaviors, health risk factors, anthropometric measures, biochemical profiles, dietary behaviors, and food and dietary intake [49]. In the first study, 3371 individuals completed the health interview, health examinations, and food frequency questionnaire (FFQ). The study population was limited to individuals >19 y of age, and for those who did not report the Patient Health Questionnaire (PHQ-9), the frequency of probiotic foods and other interviews were excluded (n = 441). Thus, 2930 individuals were included in the analysis. In the second study, we initially included 23 188 individuals who completed health interview, health examination, and FFQ. After excluding individuals who were <19 y of age (n = 3670) and who did not respond to the question for the assessment of depression and intake of probiotic foods (n = 18 768), 750 individuals were used in the analysis.

Assessment of probiotic food consumption

The FFQ was used to evaluate the consumption of probiotic foods. The FFQ used for the KNHANES included 112 food items and was evaluated with four seasonal 3-d dietary records. A detailed description of validation of the FFQ is provided elsewhere [50]. The types of probiotic food included fermented vegetables (kimchi) and fermented milk products. We did not include other probiotic foods in which live bacteria were destroyed while being processed. Using the frequency of consumption reported for probiotic foods, the probiotic food consumption group was classified into three tertiles: lowest, middle, and the highest. Information on the use of probiotic supplements was not included in the analyses because the KNHANES did not have enough data.

Estimation of depression

Depression was evaluated by two different methods, one with the PHQ-9 score and the other with a self-reported clinical diagnosis by a physician. The PHQ-9, a well-established screening tool for detection of depression [51,52], was used to assess the presence and severity of depressive symptoms. The PHQ-9 is composed of nine questions and each item was scored from 0 (*not at all*) to 3 (*nearly every day*) [51]. A total score of PHQ-9 was calculated and participants were classified into a moderate to severe depression group with PHQ-9 scores ≥10, a mild depression group with scores of ≤5 to <10, and a normal group with scores ranging from 0 to <5. Participants who did not have sufficient data on the PHQ-9 were excluded from the analyses. The definition of clinical depression was determined by answers to the question: “Have you ever been diagnosed with depression by a physician?” Individuals answered with a binary answer (yes/no). Those who answered yes were categorized into a clinical depression group and those who answered no were considered non-depression. We excluded the remaining individuals who did not answer the question. Thus, we examined the link between probiotic food consumption and the PHQ-9 score and clinically diagnosed depression.

Statistical analysis

All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA). Taking into account the complex, stratified, multistage probability-cluster survey design of the KNHANES, all statistical analyses in the present study were adjusted with stratified sampling weights.

Continuous values are expressed as mean ± SEM, and categorical values are presented as n (%). Analysis of variance was performed to compare the mean of continuous variables between probiotic food consumption groups. To compare the differences in categorical values between probiotic food consumption groups, χ^2 tests were used.

Potential confounders included age, sex, body mass index (BMI), socioeconomic status, educational level, lifestyle (smoking, alcohol use, and physical activity), overall health status, and daily energy intake. Household income was classified into four categories as follows: the lowest, lower middle, upper middle, and the highest. Educational levels were grouped into four categories as follows: elementary school or less, middle school, high school, and college or more. Smoking status was defined as follows: Smokers were those who had smoked >100 cigarettes in their lifetime and are currently smoking. The others were considered non-smokers. For alcohol consumption, drinkers were those who drank more than once a month in the previous 12 mo. Physical activity was defined by answers to the question: “How many days and time do you spend in physical activity such as

walking?" Individuals who reported more than 5 times a week and >30 min each time were considered active, whereas those who exercised but the level of physical activity did not meet the criteria were considered inactive. Overall health status was determined by subjective perception of general health: excellent, very good, good, fair, or poor. Information on daily total energy was obtained from the FFQ.

We carried out linear regression analysis to assess the association between the frequency of probiotic food consumption and PHQ-9 score. Furthermore, multiple logistic regression analysis was used to assess the association between the probiotic food consumption (the lowest, middle, the highest) and PHQ-9 group (moderate to severe, mild, normal) with unadjusted and adjusted models. We conducted multiple logistic regression analysis to examine the association between the probiotic food consumption (the lowest, middle, the highest) and clinical depression (yes/no) with unadjusted and adjusted models. We calculated odds ratio (OR) and 95% confidence intervals (CIs) based on the lowest tertile group of probiotic food consumption as a reference. In the adjusted model, confounding factors were age, sex, household income, educational level, smoking status, alcohol consumption, physical activity, overall health status, and daily total energy intake. $P < 0.05$ in two-sided tests was considered statistically significant.

Results

General characteristics of study participants

First, we aimed to identify the association between probiotic food consumption and the measure of current depressive symptoms and their severity assessed by PHQ-9 in the general population. Among 2930 individuals 19 to 64 y of age in the study of association between PHQ-9 depressive symptoms and probiotic food consumption, there were 1160 men (39.8%) and 1764 women (60.2%). We categorized individuals into tertile groups based on the frequency of probiotic food consumption. The mean frequency of probiotic food intake was 4.20, 11.29, and 19.24 times per week in the lowest, middle and the highest tertile groups, respectively (Table 1). Individuals who consumed more probiotic foods were significantly older with average ages of 39.58, 42.80, and 45.67 y in the lowest, middle, and the highest tertile groups, respectively. The sex ratio was significantly different among tertile groups ($P = 0.0066$). The frequent users in the highest tertile group showed significantly higher BMI ($P = 0.0032$) and total energy intake ($P < 0.0001$). Frequent users also had significantly less cigarette use ($P = 0.0098$). However, there were no significant differences in educational level, household income, alcohol use, physical activity, and overall health status between the groups.

Second, to investigate whether probiotic food has decisive effects on a final diagnosis of clinical depression in clinical settings, we further examined the relationship of probiotic food consumption with clinically diagnosed depression. In all, 760 individuals were diagnosed by a physician as having clinical depression in the second study for assessing the effects of probiotics on a final diagnosis of clinical depression: 145 (26.8%) were men and 615 (73.2%) were women. They were categorized into the tertile groups of probiotic food intake. Individuals exposed to more probiotic foods were significantly older ($P = 0.0001$) and showed significantly different lifestyle patterns with lower use of cigarettes ($P = 0.0303$) and higher intake of total energy ($P < 0.0001$; Supplementary Table 1).

Association between probiotic food consumption and the presence and severity of depression assessed by PHQ-9

Table 2 shows the association between probiotic food consumption and the presence and severity of depression evaluated by the

Table 1
Participant characteristics (2016)

Characteristic	Probiotic food consumption			
	T1 (lowest)	T2 (middle)	T3 (highest)	*P*-value
Participants	1098 (37.47)	853 (29.11)	979 (33.41)	
Probiotic food intake, time/wk	4.20 ± 0.07	11.29 ± 0.10	19.24 ± 0.12	<0.0001
Age, y	39. 58 ± 0.38	42.80 ± 0.41	45.67 ± 0.37	<0.0001
Sex				
Male	397 (36.16)	364 (42.67)	405 (41.37)	0.0066
Female	701 (63.84)	489 (57.33)	574 (58.63)	
BMI, kg/m^2	23.69 ± 0.12	23.67 ± 0.12	24.12 ± 0.11	0.0032
Educational level				
Elementary or less	69 (6.28)	64 (7.50)	91 (9.30)	0.2814
Junior high school	78 (7.10)	64 (7.50)	76 (7.76)	
High school	411 (37.43)	319 (37.40)	350 (35.75)	
College or more	540 (49.18)	406 (47.60)	462 (47.19)	
Household income				
Q1 (lowest)	108 (9.84)	69 (8.10)	72 (7.37)	0.3045
Q2	268 (24.41)	202 (23.71)	220 (22.52)	
Q3	344 (31.33)	282 (33.10)	314 (32.14)	
Q4 (highest)	378 (34.43)	299 (35.09)	371 (37.97)	
Smoking status				
No	885 (80.60)	663 (77.73)	816 (83.35)	0.0098
Yes	213 (19.40)	190 (22.27)	163 (16.65)	
Drinking status				
No	541 (49.27)	387 (45.37)	489 (49.95)	0.1102
Yes	557 (50.73)	466 (54.63)	490 (50.05)	
Physical activity				
No	656 (59.74)	516 (60.49)	598 (61.08)	0.8225
Yes	442 (40.26)	337 (39.51)	381 (38.92)	
Health status				
Excellent	55 (5.01)	45 (5.28)	45 (4.60)	0.1353
Very good	280 (25.50)	249 (29.19)	285 (29.11)	
Good	563 (51.28)	430 (50.41)	512 (52.30)	
Fair	169 (15.39)	116 (13.60)	119 (12.16)	
Poor	31 (2.82)	13 (1.52)	18 (33.41)	
Energy intake, kcal/d	1826.41 ± 22.05	1943.97 ± 24.64	2135.88 ± 25.79	<0.0001

BMI, body mass index
All values are n (%) or mean ± SEM. Statistical significance based on analysis of variance or χ^2 test.

Table 2
Association between probiotic food consumption and PHQ-9 depressive symptoms

	Probiotic food consumption		
PHQ-9 depressive symptoms	T1 (lowest)	T2 (middle)	T3 (highest)
Model 1*			
Normal	Reference	Reference	Reference
Mild	Reference	0.79 (0.62–1.01)	0.72 (0.56–0.91)
Moderate to severe	Reference	0.71 (0.49–1.04)	0.37 (0.24–0.58)‡
Model 2†			
Normal	Reference	Reference	Reference
Mild	Reference	0.85 (0.66–1.10)	0.80 (0.62–1.03)
Moderate to severe	Reference	0.73 (0.50–1.07)	0.37 (0.24–0.59)‡
Model 3§			
Normal	Reference	Reference	Reference
Mild	Reference	0.88 (0.67–1.15)	0.81 (0.62–1.07)
Moderate to severe	Reference	0.88 (0.57–1.36)	0.48 (0.28–0.81)‖

PHQ, Patient Health Questionnaire.
Values are odds ratio (95% confidence interval).
*Unadjusted.
†Adjusted for age and sex.
‡$P < 0.005$.
§Adjusted for age, sex, body mass index, socioeconomic status, educational level, lifestyle, overall health status, and daily energy intake.
‖$P < 0.01$.

Table 3
Association between probiotic food consumption and clinical depression

	Probiotic food consumption		
Group	T1 (lowest)	T2 (middle)	T3 (highest)
All participants (N = 760)			
Model 1*	Reference	1.13 (0.73–1.75)	0.57 (0.36–0.91)†
Model 2‡	Reference	1.07 (0.69–1.66)	0.49 (0.30–0.80)†
Model 3§	Reference	1.14 (0.70–1.84)	0.59 (0.35–0.96)‖
Men (n = 145)			
Model 1*	Reference	0.95 (0.34–2.65)	0.29 (0.11–0.77)¶
Model 2‡	Reference	0.90 (0.32–2.51)	0.25 (0.09–0.70)†
Model 3§	Reference	0.93 (0.20–4.25)	0.24 (0.06–0.92)‖
Women (n = 615)			
Model 1*	Reference	1.12 (0.76–1.98)	0.75 (0.44–1.26)
Model 2‡	Reference	1.15 (0.71–1.86)	0.67 (0.40–1.13)
Model 3§	Reference	1.24 (0.72–2.14)	0.85 (0.47–1.54)

Values are odds ratio (95% confidence interval).
*Unadjusted.
†$P < 0.005$.
‡Adjusted for age and sex.
§Adjusted for age, sex, body mass index, socioeconomic status, educational level, lifestyle, overall health status, and daily energy intake
‖$P < 0.05$.
¶$P < 0.01$.

PHQ-9 questionnaire. We conducted multinomial logistic regression analysis for the probiotic food consumption group with the severity of depression classification based on the PHQ-9 score (normal, mild, moderate to severe groups). The prevalence of depression was significantly lower in the highest tertile of probiotic food consumption (unadjusted OR, 0.37; 95% CI, 0.24–0.58; Table 2). After adjustments for age and sex, a statistical significance remained in the association between probiotic food intake and depression (adjusted OR, 0.37; 95% CI, 0.24–0.59), with the fully adjusted OR being 0.48 (95% CI, 0.28–0.81). We further conducted regression analysis for the frequency of probiotic food consumption with the continuous values of the PHQ-9 score. The frequency of probiotic food consumption was significantly associated with the PHQ-9 score ($P < 0.0001$; data not shown).

Association between probiotic food consumption and clinical depression

We investigated the association between probiotic food intake and clinical depression. The highest tertile group of probiotic food consumption had a significantly lower prevalence of clinical depression both in the unadjusted (OR, 0.57; 95% CI, 0.36–0.91) and fully adjusted models (OR, 0.59; 95% CI, 0.35–0.96; Table 3). We further conducted a subgroup analysis among men and women. Although no significant relationship was found in women, there was a strong association between probiotic food intake and depression in men with a significantly lower OR (unadjusted OR, 0.29; 95% CI, 0.11–0.77). Odds ratio adjusted for age and sex was 0.25 (95% CI, 0.09–0.70). After fully adjusting for the confounders, beneficial effects of probiotic foods on depression remained strong (adjusted OR, 0.24; 95% CI, 0.06–0.92).

Discussion

There has been substantial interest in manipulation of the gut microbial composition with probiotic bacteria regarding mental illness, suggesting the role of psychobiotics in treating mental disorders [28,29,53]. However, currently available evidences are not enough to conclusively demonstrate the effects of probiotics on mental health. Therefore, we sought to conduct a well-controlled, large population-based study for better understanding of the regulatory roles of probiotics on depression among Korean adults using the KNHANES data. We found that the intake of probiotic food is significantly associated with lower severity and prevalence of depressive symptoms measured by a PHQ-9 questionnaire. In addition, we showed a significant effect of probiotic food consumption on lower OR of self-reported clinical depression in men but not in women.

We observed higher BMI and energy intake in the frequent users of probiotic foods, which were considered as confounders in the analyses. Interestingly, frequent users of probiotic foods had healthier lifestyles with less use of cigarettes than non-frequent users. Although we cannot rule out the possibility that people with healthier lifestyles tend to be more motivated to prevent health problems including depression, probiotic effects remained beneficial in lowering the risk for depression after adjustment of health status and lifestyle. In addition, based on the present study, the average age of the highest tertile group of probiotic food intake was higher than others. We suppose that it is because older groups in the Korean population tend to have a higher intake of fermented vegetables, mainly kimchi, which is known to contain various lactic acid–producing bacteria such as *Leuconostoc, Lactobacillus,* and *Weissella* [54,55]. Therefore, we invite further research on the prevalence and severity of depression with dose–response effects of probiotics among the older population. Furthermore, there was no significant difference in total intake of probiotic foods between men and women, but we found a sex difference in OR for clinical depression. It is well established that there is a sex difference in MDDs. Thus, we have no doubt that not only environmental risk factors [56] but biological factors related to the sex differences in depression also might have contributed to the different results associated with sex in the present data [57]. Possible biological factors that resulted in the sex gap in this study may include genetic predisposition and hormonal differences [57]. It also is plausible that the sex gap was due to differences between men and women in psychopathology, including symptoms, course, comorbidity, and health consequences of depression [58,59]. Therefore, we suggest that it is important in future studies to investigate the association between probiotic food consumption and depression concerning sex-related subtypes of depression to understand the sex gap.

Possible mechanisms underlying the positive effects of probiotics on depression have been reported. Current understandings suggest that the gut microbiota might have a fundamental role in the modulation of mood disorders and behavior via different mechanisms [60,61].

Several studies demonstrated that the gut microbiota modulates systemic and gut inflammation, which is linked to psychiatric disorders. Therefore, it is well established that improvements in gut dysbiosis suppress inflammation, thereby leading to changes in brain function, behavior, and mood [62]. In addition, certain bacteria that produce neurotransmitters are known to alter neural biochemistry and thus affect mood and behavior [62–64]. Moreover, results from animal studies showed that probiotics activate the vagal nerve, a network linking the brain and gut [30,65,66]. Overall, there are more than one mechanism and pathway that link psychobiotic effects and mood, indicating that further mechanistic studies are required to clearly demonstrate anxiolytic and antidepressive effects of probiotics.

There were some limitations to this study. First, we could not take into account the use of probiotic supplements. Considering that the number of probiotic supplement users has increased tremendously, assessing the effect of probiotic supplement associated with depression merits further studies. Second, we were not able to assess the dose–response effects of live microorganisms owing to the lack of database for the content of bacteria in the foods. Moreover, in this study, we did not have enough information on the older population from which FFQ data was not collected. Because depression is a common problem in the older population, we need further analysis on the effects of probiotics on geriatric depression. In addition, the KNHANES questions about clinical diagnosis of depression are from self-reported questionnaires. This might result in misclassification bias, although the survey was conducted by trained interviewers and the questionnaire has been widely used in several studies [67–69]. Moreover, there might be possible recall bias because the depressive symptom and dietary intake measurement relied on the self-reporting of the participants. Furthermore, potential for selection bias might arise from few individuals who answered the question related to a diagnosis of depression in the second study. We suppose that the actual number of people having depression is higher than the estimated number, but they are not diagnosed yet or did not report it because of stigma.

Despite these limitations, this is the first nationwide, large population-based study showing that probiotic food consumption is significantly associated with lower severity and prevalence of depression in Korean adults. These findings provide meaningful information that probiotic food might have roles played in lowering the risk for depression in adults.

Conclusions

To our knowledge, this is the first study to suggest that probiotic food consumption is significantly linked with decreases in the prevalence and severity of depression in Korean adults. The results from the present study support the suggestion that use of probiotics could be a promising preventative strategy for depression. However, a randomized controlled trial is required to establish causal and mechanistic relationships between the roles of probiotics and mental health with comprehensive investigations of the relations between gut microbiome and moods.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2019.02.007.

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