# The Fruit in Alleviating Neurological Diseases via the Gut-Brain Axis

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**Abstract.** Fruits, as an important component of a healthy diet, not only contain essential nutrients for daily life, but also contain various bioactive substances, which have beneficial effects on human health. Currently, research on fruit function has focused on fruit and gut microbiota. The gut microbiota affects many important functions of the body through metabolism. At present, the relationship between gut microbiota and brain diseases, metabolic diseases, etc. has become a research focus. In the study of fruits and gut microbiota, researchers have found that it is mainly through regulating the composition of short chain fatty acids (SCFA). It is currently known that disorder of SCFA in the gut is one of the important mechanisms for some diseases. Mental disorders such as depression and autism spectrum disorder (ASD), are all associated with SCFA. Meanwhile, with the study of fruit and gut microbiota, it may be possible to prevent or even alleviate some neurological diseases by modifying the intake of fruits. In recent years, gut microbiota, ASD, and fruit intake have become important issue, and there are many related literature but a lack of systematic review. This paper analyzed the impact of different types of fruits on gut microbiota, as well as the disruption of SCFA caused by changes in gut microbiota in patients with neurological diseases. It also demonstrates that some bioactive substances can regulate SCFA, providing ideas for the treatment and alleviation of some diseases.

**Keywords:** Fruits, Gut microbiota, SCFA, Neurological disease, Autism spectrum disorder (ASD)

## 1. Introduction

Fruits are an indispensable part of a healthy eating pattern. The Mediterranean diet has been ranked first on the list of best diets by the U.S. News & World Report. The daily intake of the Mediterranean dietary include three to nine serves vegetables, half to two serves fruits, one to thirteen grain and eight serves olive oil[1]. Tied for second place are the DASH diet, which emphasizes fruits, vegetables, whole grains, lean proteins and low-fat dairy products, and the Flexitarian diet, which emphasizes a diet rich in plants, fruits and vegetables, and whole grains. Similarly with the Mediterranean diet, the Jiangnan diet, a kind of traditional dietary pattern of indigenous residents in the Yangtze River Basin of China, emphasize the high intake of vegetables, fruits, and coarse grains. A large number of data can prove that adhering to these dietary patterns over the long term is beneficial for people to maintain health[2]. In these healthy dietary patterns, it is essential to eat a considerable amount of fruits every day. From some dietary guidelines, it can also be seen that fruits are an indispensable part of daily diet. WHO suggests that adults should consume approximately 150g of fruit per day[3]. The dietary guidelines for Americans suggest that adults should consume 1.5 to 2.0 cup-equivalent of fruit per day[4].

The main focus of current research on fruits is on the nutrient function of the fruit, Various fruits can provide a range of nutrients and different bioactive substances, including fibre, vitamins, minerals and phytochemicals[5]. Fruit is regarded as an important source of fibre, fibre intake has been associated with a reduced incidence of cardiovascular disease and obesity. Phytochemicals play a role in antioxidant, anti-inflammatory and other protective mechanisms. However, the specific mechanism of action of these bioactive substances in the human body is still not fully understood[6].

However, more attention paid to gut microbiota due to its clinical significance[7]. There have been many studies on the relationship between food and microorganisms in metabolism, and related metabolites have a significant impact on many diseases. Existing studies mainly focuse on fruit for

constipation, diabetes, nonalcoholic fatty liver disease (NAFLD) and other digestive and metabolic diseases, with few studies on neurological diseases[8-10].

This review collects current papers on the impact of fruits on gut microbiota, and analyzes the impact of microbiota on the production of short chain fatty acids (SCFA). SCFA disorder, as one of the possible pathogenesis of neurological diseases, may provide a new way for the treatment and prevention of neurological diseases, through the regulatory effects of fruits on SCFA, and provide a new research perspective for fruit as functional foods.

## 2. Study on the Component in Fruits

Fruits contain a large amount of macronutrients and micronutrients needed by the human body. In addition to carbohydrates, proteins, lipids, organic acids, and dietary fiber, they also contain water- and fat-soluble vitamins, minerals, polyphenols, polysaccharides, and alkaloids. It is precisely because of these bioactive substances that fruits not only provide some of the nutrients that the human body needs in daily life, but also have health benefits and can even prevent or alleviate some diseases. For example, strawberry phenolic compounds have antioxidant and anti-inflammatory effects, as well as antibacterial, anti-allergic, and antihypertensive properties, and can also prevent oxidative stress-related diseases[11]. The various bioactive substances in avocado by-products, such as organic acids, phenolic derivatives, flavonoids, proanthocyanidins, terpenoids, alkaloids, saponins, acetogenins, phytosterols, etc., make avocado have antioxidant, anti-inflammatory, lipid regulating, and neuroprotective properties[12]. The nearly 48 phenolic compounds (polyphenols, flavonoids, anthocyanins, and proanthocyanidins) in pomegranate give it strong antioxidant properties[13]. The types and content of bioactive substances may vary depending on the type of fruit. The following table lists some bioactive substances in fruits.

**Table 1**. Fruits and Substance

| Fruit types | Substance contained | | | | Ref. |
|---|---|---|---|---|---|
| Banana | Carotenoids | Phenolic compounds and flavonoids | Amine compounds | | [14] |
| blueberry | From 137 to 9400mg/100g fresh weight due the genotype. Total phenolics 3517±54.8mg/100g freeae dried whole blueberries(FD) 2671±384concentrated blueberry phenolic extract (CE) | | | | [15] |
| Apple | fiber 2%-3% Insoluble fiber: cellulose and hemicullose Soluble fiber: homogalacturonans and rhamnogalacturonans | polyphenols 110.2 mg/100 g of fresh fruit and ranged from 66.2 mg to 211.9 mg/100 g | | | [16] |
| blackberry | phenolic compounds 2290.62 ± 34.48 mg GAE/100 g, per gram of dry fruit | carbohydrates 285.00 ± 10.89 mg GE/g, per gram of dry fruit | | | [17] |
| camu camu | Total polyphenols 6550±140 mg/100g dry weight | suger Glucose:1110±0.08mg/ 100g dry weight Fructose:1790±0.11mg /100g dry weight Polysaccharides 7280±5.04 mg/100g dry weight | Fibres total 34290±685.8mg/100g dry weight Insoluble 8092.44±161.8mg/100g dry weight Fibres 3669.03±73.3mg/100g dry weight | Vitamin C 3330±90.8 mg/100g dry weight | [18] |

## 3. Study on Specific Composition and Gut Microbiota in Fruits

Researches on the fruits and gut microbiota mainly focuses on the interrelationships between fruits in the gut and gut microbiota. We mainly studied the effects of fruits and different gut microbiota, as well as the related factors produced on various diseases in the body. The research on fruits focuses on bioactive substances such as polyphenols, polysaccharides, organic acids, flavonoids, terpenoids, vitamins, and alkaloids. The study found that the main factors affecting the microbial community in fruits are polyphenols, polysaccharides, oligosaccharides, anthocyanins, and flavonoids.At the phylum level, these substances mainly affect Firmicute, Bacteroidetes, Proteobacteria, and Actinbacteria. The gut microbiota metabolizes and produces SCFA in the body, and the deregulation of SCFA is one of the mechanisms underlying some diseases. Therefore, adjusting the proportion of SCFA by consuming fruits or their extracts to alter gut microbiota composition may become one of the means to prevent diseases or alleviates the symptoms of diseases.

Diet is considered an important factor affecting the quantities and species of gut microbiota. Some fruits and their active substances can promote the growth of some bacterial communities in the gut. Oral administration of Camu camu to rats can completely prevent the decrease in microbial richness caused by diet, while also preventing the increase in Firmicutes to Bacteroidetes ratio caused by diet[18]. In vitro experiments, it was found that blackberries reduced Firmicute levels from 81.46% to 32.25%, and Bacteroidetes from 6.18% to 37.14%. Significantly reduced the proportion of Firmicute to Bacteroidetes ratio[17].

The effect of fruits on the gut microbiota is mainly due to the active substances in the fruits. The study found that polyphenols in blueberries can alter the structural components of gut microbiota in rats, reducing the Firmicutes to Bacteroides ratio, and the extent of reduction is positively correlated with intake dosage. The intake of high doses (1000 mg total polyphenols per kg bw per d) of polyphenols not only increased the quantity of Proteobacteria, but also increased the abundance of Bacteroides dorei and Lachnoclostridium, but reduced gut microbial diversity. While moderate doses (250 mg total polyphenols per kg bw per d) increased gut biodiversity. This is because polyphenols are dietary hormones that are beneficial at low doses and have no or adverse effects at high doses[15]. In another study on the effects of pomegranate fruit pulp polyphenols (PFP) on the gut microbiota of rats, the changes in microbial composition were basically consistent with those of the moderate dose group of blueberry polyphenols. 200 mg/kg of PFP daily, increasing the abundance of Bacteroidetes and reducing the abundance of Firmicutes and Proteobacteria[19]. A higher proportion of Firmicutes to Bacteroides may contribute to metabolic diseases, such as obesity and diabetes[20]. The increase in Proteobacteria is a potential diagnostic feature of gut microbial dysbiosis and disease risk. Proteobacteria accounts for a small proportion of gut microbiota, but it will induce obesity and diabetes when its proportion increases[21]. For other beneficial bacteria, polyphenols also have a promoting effect. Anthocyanins, a soluble polyphenol, can stimulate the growth of Bifidobaterium spp. and Lactobacillus Enterococcus spp. These bacterial strains have positive effects in the large intestine, including the production of SCFA, competing for growth substrates and adhesion sites to resist the antibacterial effect of pathogenic bacteria, and reducing potential harmful bacteria such as Clostridium histolyticum, which are associated with promoting tumors and inflammatory bowel disease[22].

The polysaccharides in fruits also have similar effects on the gut microbiota. Longan pulp polysaccharides can reduce the proportion of Firmicutes to Bacteroidetes in rats. In vitro experiments, it was found that Longan pulp polysaccharides can significantly promote the abundance of probiotics such as Lactobacillus, Enterococcus, Bifidobacterium, and reduce the growth of harmful bacteria such as Clostridium[23]. Rosa roxburghii Tratt fruit polysaccharides reduced the Firmicutes to Bacteroides ratio in rat gut microbiota and increased the abundance of Bacteroidaceae and Lactobacillilaceae. Meanwhile, this study found that oral administration of Rosa roxburghii Tratt fruit polysaccharide could significantly reduce the body weight, liver hypertrophy, fasting blood glucose, serum insulin and lipid levels of type 2 diabetes mice[24]. This is consistent with the inferred role of the gut microbiota. Therefore, one of the action ways of active substances in fruits for metabolic

diseases such as obesity and diabetes may be achieved by changing the composition of the gut microbiota.

**Table 2**. Modulation of the gut microbiota by fruit consumption

| Type of fruit | Actual intake | Type of study | Dosage | Treatment duration | Changes in microbiota | Ref. |
|---|---|---|---|---|---|---|
| blueberry | purified extract of blueberry polyphenols | A rat model of postmenopausal estrogen deficiency | 0, 50, 250, or 1000 mg total polyphenols per kg bw per d | 90d | 50: - F:B<br>250: - F:B<br>+ richness<br>+ Rickenellaceae RC9 gut group<br>+ Eubacterium xylanophilum group<br>1000: - F:B<br>- richness<br>+ Proteobacteria<br>+ Bacteroides dorei + Lachnoclostridium<br>- Rickenellaceae RC9 gut group<br>-Eubacterium coprostanoligenes group | [15] |
| | lyophilized blueberries | | 50 mg total polyphenols per kg bw per d | | + richness<br>+ Alistipes | |
| Blackberry | The freeze-dried blackberry fruits powder | In vitro | 2.0 g | | - Firmicute<br>+Bacteroidetes<br>- F:B | [17] |
| camu camu | Extract of camu camu | male mice | 200mg/kg | 8 weeks | + richness<br>+Bifidobacterium and Barnesiella<br>- Lactobacillus<br>- F:B | [18] |
| Rosa roxburghii Tratt | polysaccharide (RTFP) purified from R. roxburghii | Male obese diabetic db/db mice and normal db/m mice | 300, 600 and 900 mg/kg/d of RTFP | 8 weeks | +Bacteroidaceae, Bacteroidaceae S24-7 group, Peptostreptococcaceae, Lactobacillus, Prevotellaceae and Rikenellaceae<br>-Enterocaccaceae, Desulfovibrionaceae, Clostridiaceae1, Clostridialesvadin BB60 group, Ruminococcaceae, Erysipelotrichoceae, Helicobacteraceae, Ruminococcaceae and Lachnospiraceae<br>900:<br>+Bacteroidales and Lactobacillus<br>-Clostridiales and Desulfovibrionales | [24] |
| Dragon fruit | Dragon fruit oligosaccharide powder | Daphnia magna | 0,9 and 27 mg l−1 DFO | | + Proteobacteria<br>+Bacteroidetes<br>+ Limnohabitans | [25] |
| | Dragon fruit oligosaccharides derived from water extraction of the flesh and peel of dragon fruit | healthy adults | group 2- dose 1 of DFO (consisting of 4 g of DFO and 4 g of maltodextrin)<br>group 3 – dose 2 of DFO (consisting of 8 g of DFO). | 4 weeks | 4g/day:<br>+Bifidobacterium adolescentis (1.4%)and Bifidobacterium catenulatum(1.12%)<br>-Faecalibacterium(6%)<br>(no change) Lactobacillus.<br>-Streptococcus salivarius(1.40%) , Streptococcus pneumonia (1.03%), Clostridium perfringens(1.62%), | [26] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Longan | Longan polysaccharide LPIIa | In vitro | 20mL LPIIa solution (6.0 mg/ mL) was blended with 20 mL artificial gastric juice | 48 h | Clostridium celatum(1.55%) Escherichia coli (2.66%) 8 g/ day : +Bifidobacterium adolescentis(0.31%), Bifidobacterium catenulatum(9.74%), Faecalibacterium prausnitzii (1.97%) -Streptococcus salivarius(3.27%), Bacteroides fragilis,(1.29%), Escherichia coli(8.43%) +Lactobacillus, Enterococcus, Bifidobacterium, Sutterella, Collinsella, Pediococcus, Dorea, and Blautia -Acidaminococcus, Desulfovibrio, and Clostridium_sensu_stricto_1 - F:B +Lachnospiracese_NK4A136_group -norank_f_Bacteroidales_S24-7_group | [23] |
| | | BALB/c mice | 50, 100, and 200 mg/kg of LPIIa | 28 days | 200:+ richness | |
| Litchi chinensis | L. chinensis seed powder (LS) L. chinensis seed ethanol extract (LSE) L. chinensis seed water extract (LSW) | Zebrafish | HLS (1.4 mg per zebrafish per day) HLSE (0.35 mg per zebrafish per day) HLSW were given using a water bath (42 mg L−1). | 8 weeks | - Cetobacterium + Lactococcusand Moraxellaceae HLS: + Mycoplasma and Trichococcus HLSW:+Lactobacillus, Faecalibaculum, Muribaculaceae, Erysipelotrichaceae and Aeromonas HLSE:+Erysipelotrichaceae and Aeromonas | [27] |
| | | mouse | NLS: :normal diet, and LS HLS: high-fat diet and LS (2 g kg−1) HLSE: high-fat diet and LSE (500 mg kg−1) HLSW: high-fat diet (300 mg kg−1) | 12 weeks | | |
| Pomegranate | pomegranate fruit pulp polyphenols (PFP) | pathogen-free male C57BL/6 J mice | 200 mg/kg of PFP daily | 14 weeks | + Bacteroidetes - Firmicutes - Proteobacteria - Escherichia coli, Lactococcus lactis, Blautia producta and Ruminococcus bicirculans +Akkermansia muciniphila, Bacteroides acidifaciens, Parabacteroides distasonis, Lachnospiraceae_bacterium 28-4, Clostridium leptum, Alistipes finegoldii, Clostridium scindens and Mucispirillum schaedleri | [19] |
| aronia berry | (poly)phenol-rich extract & whole fruit powder | Dealthy men | A (poly)phenol-rich extract (116 mg, 75 g berries) A whole fruit powder (12 mg, 10 g berries), | 12 weeks | aronia extract: +Anaerostipes whole fruit: +Bacteroides | [28] |

# 4. SCFA and Fruits

## 4.1. SCFA

SCFA in the human body are mainly produced by bacterial fermentation using undigested and absorbed carbohydrates in the gut as substrates, and a small portion comes from the fermentation of amino acids. At present, the production of SCFA is the main research content on the relationship between gut microbiota and human health. SCFA can directly regulate host metabolic health through a series of tissue-specific mechanisms related to appetite regulation, energy expenditure, glucose homeostasis, and immune regulation[29]. The disorder of SCFA plays an important role in hypertension, cardiovascular disease, NAFLD and diabetes[30-32]. In addition, there are no mature and robust methods for measuring SCFA in the human body currently, mainly relying on the measurement of SCFA in human feces. Gas chromatography/mass spectrometry is the most commonly used method for SCFA analysis in biological samples[33].

SCFA is an important product of the gut microbiota. According to existing research, the bacteria that produce SCFA at phylum level are mainly Proteobacteria, Bacteroidetes, Firmicutes, Actinbacteria, which account for up to 99% of the gut microbiota. The growth of these bacteria is correlated with intake of fruits. For example, blueberries can increase the abundance of Proteobacteria in rats[15]. Blackberries can reduce Firmicute and increase Bacteroidetes in vitro experiments[17]. Blueberries and blackcurrents can increase the number of Bacteroidetes (from 7% to 10% -12%) and Actinobacteria (from 2% to 9% -15%) in feces[34]. The bacteria that produce SCFA can be characterized through metagenomics. Different species of SCFAs produce slightly different bacterial species[35]. The most studied SCFA are acetic acid, propionate acid and butyric acid. Bacteria are an important factor affecting the production of intestinal SCFA. Scientific studies have shown that the bacterial species that can produce more SCFA are Clostridiaceae, Lachnospiraceae, Bifidobacterium, Eubacterium rectale, Eubacterium hallii, Faecalibacterium prausnitzii, and Ruminococcus bromi[36]. Different bacteria produce different SCFA. It has been found that the metabolites of Proteobacteria, Bacteroides Prevotella group (Bacteroidetes), and Bifidobacterium spp. are acetic acid and propionic acid, while butyric acid is mainly produced by Firmicutes[37]. Dysregulation of SCFA production is an important mechanism for the production of some diseases. Research have found changes in gut microbiota and SFCA in patients with immune and neurological diseases. Studies have demonstrated that patients with celiac disease have changes in their gut microbiota, and compared to normal subjects, there is an increase in Proteobacteria and other unknown bacterial phyla in their gut and fecal microbiota. Proteobacteria is positively correlated with production of propionate and acetate production, so is the total SCFA[37]. Proteobacteria, Bacteroides-Prevotella group (Bacteroidetes) and Bifidobacterium spp. are considered producers of propionate and acetic acid[38]. In another study, treatment with Astragalus mongolicus polysaccharides resulted in a decrease in the proportion of Firmicutes to Bacteroides in the gut microbiota of rats, an increase in Proteobacteria and Epsilobacteria abundance, and almost no effect on fecal total SCFA. However, it is not clear the changes of each component in total SCFA. This indicates that changes in gut microbiota may not necessarily cause changes in total SCFA[39]. Excessive acetic acid has potential pro-inflammatory effects, which may be one of the factors contributing to the pathogenesis of celiac disease, an immune disease[37]. However, it is worth noting that in some cases, increasing acetic acid content has a alleviating effect on some diseases. In acute pancreatitis, the acetate produced by Paraacteroides reduces neutrophil infiltration, which may be beneficial for the treatment of acute pancreatitis[40].Alleviating dextran sulfate induced colitis can be achieved by regulating the ratio of Firmicutes to Bacteroidetes through L. acidophilus and increasing the level of protective acetate[41]. The pro-inflammatory and protective effects of acetic acid may be caused by different levels of content, or due to different disease mechanisms.

### 4.2. Autism spectrum disorder (ASD) and SCFA

The relationship between neurological diseases and gut microbiota is currently a research focus in neuroscience, and it has been shown that the metabolites of gut microbiota have an impact on brain system function. ADS is a complex neurological disease, and the mechanism of its occurrence is currently unclear. At present, research has found that the influence of bacterial species on SCFA has also been confirmed in comparative experiments between ASD patients and normal individuals. Compared to the control group, the abundance of Firmicute in the intestines of patients was lower, while Acidobacteria showed enrichment. Firmicute is the main bacterial group that produces butyrate. Acidobacterium is positively correlated with the production of valeric acid, resulting in lower levels of butyrate and higher levels of valeric acid in the feces of patients with ASD compared to those with normal nerves. Additionally, acetic acid levels in the feces of ASD patients are lower[42]. However, in other studies on ASD, there are different conclusions about the amount of Firmicute in the patient's intestine. Lucia et al analyzed 18 studies and found that Bacteroidetes, Firmicutes, and Actinobacteria were more abundant in children with ASD, with lower levels of Coprococcus and Bifidobacterium compared to normal children.[43]. Carlo et al. found that a decrease in the proportion of Bacteroidetes/Firmicutes results in a decrease in the abundance of Bacteroidetes[44]. From the perspective of SCFA, there are also some discrepancies in other studies. James et al. found that compared to normal children, children with ASD have significantly lower levels of total SCFAs, including acetate, propionate, and valerate. Low Bifidobacter levels and high Lactobacillus levels in ASD patients[45]. According to the study by Ying et al., the levels of Bifidobacteriales and Bifidobacterium in ASD patients are lower, while the levels of acetic acid, propionic acid, and butyric acid are significantly lower, which is consistent with the results of James et al.'s study[46]. A large amount of evidence proves that the gut microbiota and its metabolite SCFA in ASD patients are closely related to their pathogenesis. The difference in levels of microbiota and SCFA may be due to factors such as experimental subjects, research design, and detection methods. For example, the gut microbiota of young children is still unstable[47]. It may also be the method variation caused by different experimental methods and different instruments, which will affect the results. Further studies are therefore needed to determine the exact changes in gut microbiota in relation to ADS[48].

### 4.3. SCFA and Fruits

The disruption of SCFA produced by gut microbiota plays a crucial role in diseases, and scientists are currently searching for ways to regulate SCFA by improving gut microbiota through dietary changes. As an important dietary source, fruits are expected to become one of the means to change SCFA. A study found that the concentrations of acetate, propionate, butyrate, and total SCFA in the cecum of obese rats were significantly higher than those in the control group after consuming Bruguiera gymnorhiza fruit flow (BGF). And the degree of increase in the concentration of each component is positively correlated with the concentration of BGF intake. The concentration of each SCFA at an intake dose of 4 g/200 g BW/day is comparable to the intake of orlistat (30 mg/kg BW/d), indicating that the metabolites regulating the gut microbiota by BGF treatment are acetate, butyrate, and propionate[49]. Passion fruit peel (PFP) is a fruit by-product. Research has found that PFP can significantly increase the diversity of microorganisms and the content of butyrate in the cecum of Sanhuang chicken[50]. Similar results were also obtained in the in vitro fermentation experiment of mulberry polysaccharides, with a significant increase in total SCFA, acetic acid, propionic acid, and butyric acid compared to the control group's fecal culture[51]. In the in vitro colon fermentation simulation of juçara pulp (Euterpe edulis), it was found that the production of acetate and propionate increased, the content of butyrate was lower, Bifidobacterium spp. Bacteroides spp. significantly increased, and Lactobacillus/Enterococcus spp. showed no significant changes. The changes in microbiota can basically explain the changes in SCFA accordingly[52]. However, there are differences in the changes in butyrate compared to the above studies, which may be due to the different types and contents of active substances contained in different fruits, resulting in differences in the impact on gut microbiota and the production of SFCA.

## 5. Summary

There are significant differences in the constant element and trace elements contained in different types of fruits, so the effects of different types of fruits and their by-products on the gut microbiota may vary, and even have completely opposite effects. Different types of gut microbiota produce different SCFA, and SCFA dysregulation is one of the pathogeneses of some neurological diseases. Therefore, it may be possible to regulate the production of SCFA by gut microbiota by changing the amount and type of fruit intake in the diet to prevent, delay, or even treat the disease. However, there are still some issues that need to be addressed urgently. Different studies have completely opposite conclusions regarding the content of SCFA in the intestines of children with ASD. This may be due to differences in detection methods, instability of gut microbiota in young children, or experimental subjects. More strict control is needed for these variable parameters. At the same time, it is still necessary to explore the optimal proportion and amount of fruit intake to regulate the production of SCFA by gut microbiota and delay the onset of neurological diseases by regulating the intake of fruits in the diet.

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