Exploring the Fermentation-Driven Functionalities of Lactobacillaceae-Originated Probiotics in Preventive Measures of Alzheimer’s Disease: A Review

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Abstract: Alzheimer’s disease (AD) is an ascending, neurodegenerative disorder that attacks the brain’s nerve cells, i.e., neurons, resulting in loss of memory, language skills, and thinking and behavioural changes. It is one of the most common causes of dementia, a group of disorders that is marked by the decline of cognitive functioning. Probiotics are living microorganisms that are beneficial for human well-being. They help in balancing the extent of bacteria in the gut and support the defensive immune system of the body. Studies have found that probiotics can help with a variety of conditions, including mental health. Probiotics are beneficial bacteria that can help to maintain and strengthen a healthy gut microbiome. The gut microbiome is important for healthy brain function, as it is linked to the production of neurotransmitters and hormones that regulate mood and behaviour. This review article includes detailed review on the origination of probiotics and its significance in the treatment of AD.

Keywords: probiotics; Alzheimer’s disease; nervous system; brain cells; immune cells

1. Introduction

The concept of functional food is discussed thousands of times on different platforms [1]. Although the accurate definition is still a mystery, experts normally concur that in general, additives are involved in functional foods (containing microbes such as probiotics, mentioned underneath), which hold the benefit of health along with the basic nutrient content of the food as well (Figure 1). Functional foods have the potential to improve physiological mechanisms and enhance neuronal functioning at the level of the gastrointestinal tract (GIT) via altering biochemical parameters. Probiotics are considered one of the primary pathways for health benefits and are included in functional foods. It has been demonstrated that the host’s energy supply is significantly affected by the activities of microbiota present in the gut. The GI microbiota is the total population attributed to live microorganisms that inhabit a host organism’s GI tract [2].

Jäger et al. [3] stated that probiotics comprises of living microbes that, once ingested in sufficient quantities, are good for human health. The Greek words “pro” and “biotic”, which both imply “life”, are the origin of the phrase “probiotic” [3]. These microscopic organisms, which are primarily bacteria but can also incorporate certain yeasts, exist naturally in our own bodies as well as in certain foods and dietary supplements. The microbial community or microbiome, which consists of billions of bacteria, inhabits in the human body. It also exists in other parts, including the mouth, genital tract, and skin, but microbes are mostly found in our digestive system. Our general health is maintained by this intricate ecology [4]. The cornerstone of our health is made up of these live nutrients. Dental disease, yeast infections, eczema, and food allergies are prevented and treated by maintaining a healthy microbiome. Probiotics are a broad category of microbes. All of them have unique advantages, although the majority belong to just two groups. *Lactobacillaceae* is the most widely used probiotic. It is found in yoghurt and other fermented foods. Countless varieties may aid those who struggle to digest the milk sugar lactose as well as those who experience diarrhoea [5]. *Bifidobacterium* is frequently discovered in various dairy products and could lessen the symptoms and signs of irritable bowel syndrome (IBS) and a few other disorders [6,7]. Probiotics encompass the yeast *Saccharomyces boulardii*. It seems to aid in the prevention of diarrhoea and other intestinal problems. Slightly over 4 million (1.6%) American adults reported using probiotics or prebiotics in the previous 30 days, according to the 2012 National Health Interview Survey (NHIS). Probiotics and prebiotics were the third most popular dietary supplement among adults beside vitamins and minerals. From 2007 to 2012, consumption of probiotics in adults increased by four times. The 2012 NHIS also revealed that 300,000 children between the age of 4 and 17 (or 0.5% of the population) reported using probiotics or prebiotics in the 30 days prior to a questionnaire [8].

Probiotics have demonstrated potential for an assortment of medical conditions, such as the management of infant colic, the prevention of necrotizing enterocolitis and sepsis in premature infants, the treatment of periodontal disease, and the induction or maintenance of remission in ulcerative colitis [9]. An unbalanced microbiota in the gut that causes the alteration of the microbiome (dysbiosis) has been strongly associated with psychological disorders. The gut produces several neurotransmitters that are linked to anxiety and depression symptoms, including the neurotransmitters glutamate, serotonin, and GABA.
Numerous mental diseases are believed to be associated with gut dysbiosis, and there is strong evidence linking gut health with psychological wellness. One of the main characteristics and pathological traits linked to a wide range of neurodegenerative illnesses, including Alzheimer’s, Parkinson’s, and Huntington’s diseases, is neuroinflammation such as microgliosis and astrogliosis. Furthermore, owing to the constant presence of inflammation in the brain, classic neuroinflammatory illnesses like multiple sclerosis clearly highlight the significance of neuroinflammation in these neurodegenerative diseases. The most prevalent dementia amongst them is AD, which may be identified by an increase in neurofibrillary plaque build-up in the brain. There is strong evidence that GM (gastrointestinal microbiota) plays a role in the pathogenesis of AD, which is largely mediated by altered microglial activity in the brain. AD is just one neurodegenerative condition where microglial dysfunction has been identified [10].

The “gut–microbiota–brain axis” is a term coined for representing such relationship: a link uniting the gut microbiome and AD and also representing the role played by inflammation in the progression as well as onset of AD. The considerably discussed topic of the microbiota–gut–brain axis holds that the gut microbiota has an impact on the activities of central nervous system (CNS) [11–13]. By encouraging the development of advantageous microbes, a diet high in prebiotics supports the health of the digestive system. Throughout the fermentation of prebiotics, short-chain fatty acids (SCFAs) including butyrate, acetate, and propionate are created. They are crucial for maintaining metabolic and intestinal health. Likewise, according to the study, probiotics affect brain function and behaviour, and knowledge of these biological causes may help to improve psychological well-being in both healthy people and, possibly, those with mental illnesses [11]. Probiotics have been shown to enhance stress response, improve memory function, and even lessen anxiety and sadness in preclinical experiments with rodents [14,15].

Many theoretical concepts have been proposed regarding the contribution of the gut microbiota to AD chronic neuroinflammation. The highly significant concept includes the following ideas: (1) A neuroinflammatory condition in the brains of patients with AD that can be caused by direct microorganism infection; (2) an age-related dysbacteriosis that hypothesizes the aging immune system to be a cause of AD development; (3) a microbicidal safeguard theory indicating the immune reaction against the build-up of harmful bacteria as the cause of build-up of AD in brain; and A notable, promising result in the decrement of the progression of AD is observed when probiotics are taken as a sole supplement. The key driving force behind the exploration of overall therapeutic efficacy is now their clinically tested anti-inflammatory effects and antioxidant capabilities and their capacity to improve a patient’s cognitive function [16]. Fermented milk has the potential to be used in the treatment of mental and functional CNS disorders as well as modulating stress adaptivity and mood in disease and well-being [17]. Various foods with probiotic activity are being created from the dairy products that are fermented, including yogurt, dairy serums, and kefir containing Lactobacillaceae and Bifidobacterium [18,19].

Role of Psychobiotics in the Improving Mental Health

Probiotics, in particular psychobiotics, have demonstrated promise for treating AD and other mental health problems. These substances have a significant impact on cognitive and emotional functions as well as brain function. The gut microbiota has been linked to mental diseases including AD, and dysbiosis in the gut microbiota has been linked to brain maturation and neurogenesis. Psychobiotics can assist in re-establishing a healthy balance of gut flora, which may have a good impact on AD symptoms and cognitive performance [20]. Psychobiotics have been shown to have anti-inflammatory properties, and by controlling the immune system and blocking the production of inflammatory substances and chemicals, they can reduce neurological inflammation. By lowering neuroinflammation, psychobiotics may save brain cells and slow the onset of AD. It has been shown that neuroprotective substances like brain-derived neurotrophic factor (BDNF), which promotes the development and longevity of neurons, are produced by some psychobiotics. Since

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inadequate amounts of BDNF have been associated with AD, boosting BDNF synthesis by using psychobiotics may aid in preserving the health and functionality of neurons. The capacity of the stomach to create and employ neurotransmitters like serotonin and gamma-aminobutyric acid (GABA), which are essential for regulating emotions, cognition, and recollection, may be impacted by psychobiotics [21]. By altering neurotransmitter levels, psychobiotics may improve cognitive performance and emotional well-being in persons with AD. Increased intestinal permeability, a side effect of AD, facilitates the bloodstream entry of harmful substances and can lead to cognitive decline. Psychobiotics have been shown to boost the intestinal barrier’s capacity to prevent the entrance of contaminants by promoting the production of mucins and tight junction proteins. By enhancing gut barrier function, psychobiotics may aid in the reduction in systemic inflammation and may improve memory retention in AD [22]. Oxidative stress is one of the key elements in the development and progression of AD. Psychobiotics are antioxidants that can scavenge free radicals to decrease oxidative damage to brain cells. By reducing oxidative stress, psychobiotics may help to preserve neurons and decrease the neurodegenerative processes linked to AD [23]. Psychobiotics therapies may improve emotional behaviour and cognitive performance in children and adolescents, according to a comprehensive review by [24]. Another study by Cheng et al. [25] discovered that certain psychobiotic strains reduced cortisol levels and suppressed inflammation, which improved the signs and symptoms associated with anxiety and depression.

2. Production of Probiotics from Dairy and Non-Dairy Products

Generally, probiotics play a crucial role in the development of the human body, including digestive systems, mental disorders, immunological disorders, and so on. They can be found in many dairy and non-dairy products and are considered to have several health advantages. Kefir and yoghurt are two dairy products that are widely recognized for their probiotic properties [26,27]. Probiotics are formulated by fermenting milk with certain bacterial strains such as Lactobacillaceae and Bifidobacterium. Lactose, a natural milk sugar, undergoes fermentation and is transformed into lactic acid. This trims down the product’s pH and creates the acidic environment required for the enhancement of valuable microorganisms. Dairy probiotics are made by several processes [28]. To get rid of dangerous microorganisms, milk is first pasteurized. The milk is then infused with the specific strains of microbes, and then, the milk is kept at a particular temperature to encourage bacterial development. The bacteria break down the lactose in the milk during fermentation to generate lactic acid, which gives the final product its distinctively sour flavour [29]. Non-dairy probiotic supplements are a great alternative for people who are intolerant to lactose or consume a plant-based diet. Probiotics that are non-dairy can be made from coconut, soy, and almond milk, among other sources. Dairy probiotics are produced using identical fundamental principles, but certain alterations are needed to account for the distinctive properties of non-dairy components. One common method of producing non-dairy probiotics is using starter cultures. Using starter cultures is one popular technique for creating non-dairy probiotics. Starter cultures are combinations of certain bacterial strains that are introduced to non-dairy products. These cultures have been chosen because of their propensity to successfully ferment milk and generate favourable microbial strains. The gratification and nutritional accessibility of non-dairy products might vary, as the fermentation process for non-dairy products may take longer than for dairy products [30,31].

According to da Silva et al. [32], fermentations of cereal and fruit have a lot of potential for developing new probiotic drinks. The scientific community has performed in-depth investigations on several substrates, including mango, blueberry, orange, cherry, apple, and pineapple, either separately or in combination. It is important to recognize the various nutritional and health-enhancing advantages that grains and fruits offer. For the manufacturing of non-dairy probiotics, other methods such as freeze-drying, starter cultures, and encapsulation are also active. Probiotic cultures can be freeze-dried to extend their ability,
to remove moisture, and extend shelf life. Encapsulation entails covering the probiotic bacteria in a barrier to protect them from the hostile environment of the gastrointestinal tract. They can improve a variety of biological processes when used in conjunction with probiotics, as shown in Table 1 below, which depicts the various dairy and non-dairy probiotic strains and their effect on human health, including mental health. The development of probiotic-infused non-dairy fermented drinks shows an increasing trend in the functional food industry. However, compared to its dairy-based predecessors, this field’s research is still in its infancy. Therefore, substantial research examining probiotic strain adaptability to plant environments is necessary and must be carried out [32].

Figure 2. Diagrammatic representation of process of generating probiotics from dairy and non-dairy products.
<table>
<thead>
<tr>
<th>Bacterial Strain</th>
<th>Dairy-Based Probiotics</th>
<th>Non-Dairy-Based Probiotics</th>
<th>Mechanisms</th>
<th>Effects on Mental Health</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillaceae acidophilus</td>
<td>Commonly found in yogurt and fermented dairy products</td>
<td>Found in non-dairy sources like fermented non-dairy beverages</td>
<td>Regulation of neurotransmitters, modulation of the gut-brain axis, and reduction in inflammation</td>
<td>May reduce symptoms of anxiety and depression; improves mood and cognitive function</td>
<td>[28,33–35]</td>
</tr>
<tr>
<td>Lactobacillaceae casei</td>
<td>Frequently present in dairy-based probiotics like yogurt</td>
<td>Also found in non-dairy probiotics</td>
<td>Modulation of neurotransmitters and improvement of intestinal barrier function</td>
<td>Potential to alleviate symptoms of stress, anxiety, and depression</td>
<td>[31,36,37]</td>
</tr>
<tr>
<td>Lactobacillaceae rhamnosus</td>
<td>Found in dairy-based probiotics such as yogurt</td>
<td>Also present in non-dairy probiotics</td>
<td>Modulation of neurotransmitters and enhancement of GABA receptor function</td>
<td>May reduce symptoms of anxiety and stress and improve mood</td>
<td>[35,38,39]</td>
</tr>
<tr>
<td>Bifidobacterium infantis</td>
<td>Often included in dairy-based probiotics like yogurt</td>
<td>Also used in non-dairy probiotic formulations</td>
<td>Regulation of neurotransmitters and reduction in inflammation</td>
<td>Potential to improve mood and reduce symptoms of depression and anxiety</td>
<td>[40,41]</td>
</tr>
<tr>
<td>Bifidobacterium longum</td>
<td>Commonly found in dairy-based probiotics like yogurt</td>
<td>Also used in non-dairy probiotic formulations</td>
<td>Regulation of neurotransmitters and modulation of the gut-brain axis</td>
<td>May have positive effects on mood, stress reduction, and cognitive function</td>
<td>[42,43]</td>
</tr>
<tr>
<td>Saccharomyces boulardii</td>
<td>Non-dairy probiotic commonly used in supplements</td>
<td>Frequently used in non-dairy probiotic formulations</td>
<td>Modulation of neurotransmitters and enhancement of intestinal barrier function</td>
<td>May have a positive impact on mental health and gastrointestinal disorders</td>
<td>[44,45]</td>
</tr>
<tr>
<td>Bacillus coagulans</td>
<td>Found in dairy-based probiotic products like yogurt</td>
<td>Also used in non-dairy probiotic formulations</td>
<td>Production of neurotransmitters and modulation of the immune system</td>
<td>Potential to support mental well-being and reduce anxiety</td>
<td>[46,47]</td>
</tr>
<tr>
<td>Lactococcus lactis</td>
<td>Frequently used in dairy-based probiotic formulations</td>
<td>Not commonly used in non-dairy probiotics</td>
<td>Production of neurotransmitters and modulation of the immune system</td>
<td>Limited studies on mental health effects</td>
<td>[48,49]</td>
</tr>
<tr>
<td>Streptococcus thermophilus</td>
<td>Commonly found in yogurt and other dairy products</td>
<td>Not typically used in non-dairy probiotics</td>
<td>Not extensively studied for mental health effects</td>
<td>Limited studies on mental health effects</td>
<td>[50,51]</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>Often present in dairy-based probiotics like fermented milk products</td>
<td>Also found in non-dairy probiotics</td>
<td>Not extensively studied for mental health effects</td>
<td>Limited studies on mental health effects</td>
<td>[52,53]</td>
</tr>
</tbody>
</table>
Probiotics emitted from dairy products all contain essential nutrients and minerals, like protein, vitamin D, and calcium. For healthy teeth and bones, calcium plays a vital role, and its absorption requires vitamin D, both of which are present in milk. To build body and mend muscles, we need protein [54]. Dairy products also include minerals such as phosphorus and potassium as well as the vitamins B12, B2, and A. Together, these nutrients assist to maintain healthy skin, a strong immune system, and good bone health. Conversely, non-dairy products made from plant-based milks (such as soy, almond, and coconut) and cheese and yoghurt substitutes are accessible for people who are unable or prefer not to ingest dairy owing to lactose intolerance, allergies, or dietary restrictions. Alternatives to dairy milk are frequently enriched with calcium and vitamin D, making them equally as nutrient-dense as dairy milk. They provide diversity and accommodate customers with certain dietary needs or preferences, such as lactose-free or vegan customers. In comparison to dairy products, non-dairy foods frequently have lower levels of cholesterol and saturated fat. People who are concerned about their heart health or who want to consume less saturated fat may find this helpful [55]. Plant-based replacements could provide extra nutrients like antioxidants and dietary fibre that are good for digestion and general health.

The decision between dairy and alternatives to it ultimately comes down to personal tastes, dietary requirements, and health objectives [56]. Both dairy and non-dairy ingredients may be used to make probiotics, providing alternatives for those with various dietary preferences. Specific bacterial strains, fermentation, and occasionally extra processes like freeze-drying and encapsulation are all used during the manufacturing process. Consuming probiotic foods, whether they come from dairy or non-dairy sources, might enhance digestion, and boost the immune system, among other positive health effects [57].

3. Comparison of Probiotics Originated from Lactobacilli and Other Strains

The probiotics fabricated from *Lactobacilli, Enterococcus, Bifidobacterium*, and *Clostridium butyricum* all have beneficial repercussions on health. The tough acidic environment of the stomach is naturally suitable for lactobacillus strains to thrive and colonise. They contribute to the preservation of a balanced gut microbiota by generating lactic acid, which makes it difficult for dangerous bacteria to grow [58]. Lactobacillus strains aid in microbial balance restoration and the development of advantageous bacteria, which improves digestion and nutrient absorption. Immunological responses are significantly influenced by the health of the gut, and Lactobacillus strains have been proven to boost immune system responses. They increase immune cell activity, promote antibody synthesis, and control inflammation. Lactobacillus strains can decrease the risk of infections and enhance general immunological health by enhancing the immune system’s performance [59]. In parallel to the other probiotics, lactobacilli offer certain advantages and distinctions. It is generally known that lactobacilli can endure the stomach’s acidic environment as well as the bile salts found in the small intestine. Due to this ability for resistance, lactobacilli can enter the intestines alive and start working with strong efficiency [60,61]. Some probiotics, including *Enterococcus*, might not be as resistant to bile and acid. The gut lining can be colonised and adhered to by lactobacilli, creating an obstacle that keeps infections out. This colonisation assists lactobacilli in growing more firmly in the gut, which could boost their proficiency [62,63]. In terms of colonisation competencies, *Bifidobacterium* and *Enterococcus* are comparable, although *Clostridium butyricum* can have different modes of action. The propensity of lactobacilli to create lactic acid by fermenting carbohydrates is quite strong. A healthy microbial equilibrium is encouraged by the acidity of the gut surroundings, thereby rendering it unsuitable for pathogenic bacteria [64,65]. *Bifidobacterium* can also create lactic acid, whereas *Enterococcus* and *Clostridium butyricum* have different metabolic assets. A healthy immune response has been demonstrated to be promoted by the lactobacilli’s modulation of the immune system. They may enhance the functioning of our immune response and encourage generation of special immune cells, both of which contribute to the maintenance of a healthy immune system [66]. Even though *Bifidobacterium* and *Enterococcus* are additional probiotics that may potentially have immunomodulatory properties, still
lactobacilli still boost the immune system in a more efficient manner. In Table 2 below, the difference between Lactobacillus-originated probiotics and probiotics originated from other bacterial strains is detailed for better understanding.

Table 2. Comparison between the probiotics originated from Lactobacillus and other bacterial strains.

<table>
<thead>
<tr>
<th>Lactobacillus-Originated Probiotics</th>
<th>Probiotics Originated from Other Bacterial Strains</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widely accepted and high consumer demand</td>
<td>Limited consumer demand and niche markets</td>
<td>[67,68]</td>
</tr>
<tr>
<td>Extensively studied and approved for use</td>
<td>Varies depending on the strain and region</td>
<td>[69,70]</td>
</tr>
<tr>
<td>Compatible with various processing technologies</td>
<td>Compatible with specific processes</td>
<td>[71]</td>
</tr>
<tr>
<td>Can have a relatively long shelf life</td>
<td>Varies depending on the strain and formulation</td>
<td>[72,73]</td>
</tr>
<tr>
<td>Well-documented and broad range of benefits</td>
<td>Specific benefits with less research support</td>
<td>[74,75]</td>
</tr>
<tr>
<td>Dairy-based products, fermented foods, and supplements</td>
<td>Niche products and specific dietary preferences</td>
<td>[76]</td>
</tr>
<tr>
<td>Established manufacturing processes</td>
<td>May require optimization for commercial production</td>
<td>[67]</td>
</tr>
</tbody>
</table>

A wide variety of lactobacilli strains are available, providing flexibility in probiotic formulations and uses. Diverse lactobacilli strains may have unique characteristics and functions that enable targeted therapies for a range of medical problems [77]. Due to the variety of strains, it is possible to choose the best lactobacilli-based probiotic depending on the situation. The success of a probiotic is dependent on several variables, including the strain, dose, and particular medical circumstances [78]. There are many advantages to taking different Lactobacillus strains, but it is vital to keep in mind that an appropriate composition and strain must be utilised to achieve the intended results. The characteristics and functions of various Lactobacillaceae species and strains differ. A probiotic’s effectiveness is also influenced by the bacteria’s dosage, stability, and survivability [79].

4. The Effects of Fermentation on Probiotic-Generating Microbiota

Fermentation plays a significant role in the synthesis of probiotics by fostering an environment that promotes the emergence and development of advantageous microorganisms. Fermentation influences probiotic-forming microbes by providing a favourable environment for their growth, initiating competition with other microorganisms, promoting metabolic interactions, and enhancing the survival and stability of probiotic strains. The composition and interactions within probiotic communities established during fermentation can influence the health benefits, as they are helpful in gut colonization potential and synergistic effects on the host [80]. Fermented foods and beverages often require the addition of specific starter cultures, which are composed of selected strains of beneficial microorganisms, including probiotics. These starter cultures initiate the fermentation process and establish a community of microorganisms that contribute to the development of desirable flavours, textures, and health benefits. During fermentation, the selected probiotic strains in the starter cultures compete with other microorganisms present in the food substrate [44,81]. The conditions of fermentation, such as the pH, nutrient availability, and oxygen levels, are often optimized for the growth of probiotics, giving them a competitive advantage over harmful or undesirable microorganisms. This competition helps to establish and maintain a dominant population of probiotics in fermented products. Different strains of probiotics within a community can interact metabolically during fermentation. For example, some probiotic strains may produce metabolites or enzymes that provide benefits to other strains, promoting their growth and activity. These metabolic interactions can enhance the overall probiotic effect of the microbes and contribute to the development of unique characteristics in the fermented product [82]. Probiotic-producing microbes in fermented foods often consist of multiple strains that complement each other’s functionalities. These strains may have different metabolic capabilities, including the breakdown of specific nutrients or the production of bioactive compounds. By working together, the probiotic community can have a broader range of health benefits and significantly impact the host in a positive way. Fermentation can improve the survival and stability of probiotic-
producing microorganisms. The controlled conditions of fermentation, such as low pH and the absence of oxygen, can help in the protection of probiotic strains from environmental stress and extend their shelf life. This is particularly important for probiotic viability during storage and transit, ensuring that an adequate number of viable microorganisms reached the consumer [83]. Probiotic microbiota established during fermentation can have implications for gut colonisation. When consumed, these microbes can reach the digestive system and potentially colonise the gut, contributing to the restoration or maintenance of healthy gut microbiota. The ability of probiotics to survive the harsh conditions of the gastrointestinal tract and adhere to intestinal surfaces is crucial for their colonisation potential and long-term health benefits [84].

An anaerobic metabolic process called fermentation enables the synthesis of energy when oxygen is scarce. During the fermentation process, carbohydrates are oxidised to produce a variety of by-products, such as carbon dioxide organic acids, and alcohol. The phosphotransferase system (PTS) helps in the translocation of glucose through the membrane, which is utilised in the glycolysis pathway to create pyruvate. This route metabolizes NAD+ and produces energy. Pyruvate is then transformed into L- and D-lactate by the stereospecific NAD-dependent lactate dehydrogenases (LDHs), low-density lipoprotein (LdhL) and lactate dehydrogenase D (LdhD), respectively, which replenish NAD+ and maintain the redox equilibrium. A specific kind of fermentation called lactic acid fermentation is carried out by bacteria called lactobacilli, which produce lactic acid as a by-product [85]. A significant amount of investigation has been performed on the possible health benefits of lactobacilli. When lactobacilli are found in fermented foods, they can function as probiotics and offer several advantages [86].

These are a few ways in which fermentation influences the production of lactobacilli, as discussed below.

4.1. Increased Viability
Lactobacilli can grow and survive better in environments produced by fermentation. The development of these bacteria is supported by the controlled factors of fermentation, such as temperature, pH, and the availability of nutrients, ensuring their survival [87,88].

4.2. Metabolic Activity
During fermentation, lactobacilli break down the sugars in the food substrate to produce lactic acid. The characteristic tart flavour and acidic pH of foods that have undergone fermentation are a result of this metabolic process. Food safety is enhanced by the acidic environment that lactobacilli provide by helping to stop the growth of dangerous germs and diseases [89].

4.3. Increased Availability of Nutrients
Proteins and complex carbohydrates in the food substrate are broken down during fermentation into simpler, more easily absorbed forms. Enzymes produced by lactobacilli assist in the digestion of certain nutrients, making them easier for the digestive system to absorb [90].

4.4. Bioactive Molecule Synthesis
Lactobacilli can produce a variety of bioactive chemicals via fermentation. For instance, they can generate enzymes, antibacterial compounds, and vitamins (such as vitamin K and specific B vitamins), which enhance the nutritive value of fermented foods [91,92]. There are two lactic acid bacteria (LAB) routes for fermentation, as explained in Figure 3.

By modifying environmental factors like pH, glucose content, and resource constraint, one can modify the homofermentative state of Lactococcus [89]. To make cheese, thermophilic strains of Lactobacillaceae helveticus are also employed. Streptococcus salivarius, Lactobacillaceae acidophilus, and Lactobacillaceae delbruckii are some of the homofermentative bacteria utilised in the yoghurt business. Other homofermentative bacteria employed in
the milk industry include Streptococcus spp., Enterococcus, Pediococcus, and Aerococcus, albeit they are rarely utilized as starter cultures. The detection of CO₂ gas is a requirement for heterofermentative bacterial testing. They are infrequently employed as starter cultures in the dairy business despite being uncommon in the milk and dairy industries [93]. Heterofermentative bacteria can occasionally result in flaws like slits in hard cheeses and bulging packaging in other dairy products if they enable development in considerable quantities. Leuconostoc spp., Lactobacillaceae brevis, Lactobacillaceae fermentum, Lactobacillaceae reuteri, Lactobacillaceae plantarium, Lactobacillaceae casei, and Lactobacillaceae curvatus are a few examples of heterofermentative bacteria. LAB that creates ethanol/acetic acid and CO₂ instead of lactic acid as by-products of the fermentation of glucose are known as heterofermentative bacteria. The main distinction between homofermentative and heterofermentative bacteria is already mentioned in Figure 3 [94]. The dairy industry frequently uses starter cultures for homofermentative bacteria. On the contrary, the dairy sector employs starter cultures of heterofermentative bacteria occasionally. As the by-product of hexose metabolism during glycolysis, homofermentation almost exclusively yields lactic acid. In contrast, the phosphoketolase route is used in heterofermentative process to produce equimolar levels of lactic acid, carbon dioxide, ethanol, and acetate from hexose. Facultative heterofermenters adopt this route. In facultative heterofermentative Lactobacillaceae, hexoses are essentially converted to lactic acid by the Embden–Meyerhof–Parnas (EMP) route. While Lactobacillaceae acidophilus is categorized as an obligatory homofermentative member of the Lactobacillaceae, where over 85% of hexoses are fermented to lactic acid by the glycolysis pathway, Lactobacillus casei, Lactobacillaceae rhamnosus, Lactobacillaceae paracasei, and Lactobacillaceae plantarium are defined as facultative heterofermenters [95].

**Types of Lactic acid fermentation**

![Diagram of types of lactic acid fermentation](image)

**Figure 3.** Schematic representation of types of lactic acid fermentation.

A pH between slightly acidic and neutral is required for homofermentative LAB to ferment glucose. Low pH, however, inhibits cellular metabolism and, as a result, lactic acid generation. At lower than pH 4, a huge number of LAB cannot grow [96]. Two methods are employed to maintain cell survival.
To maintain a pH of 7, lime is frequently added to the fermenters, which results in the production of calcium lactate (>90% of the lactic acid). The calcium-lactate-containing broth undergoes fermentation before being acidified with sulfuric acid to produce lactic acid. High sulphuric acid consumption results in higher levels of insoluble calcium sulphate in the form of gypsum than is produced by lactic acid as well as issues with waste disposal, additional corrosion issues, and a substantial cost in the process of recovering the product in commercial operations. In a perfect world, microbial fermentation would occur in a medium whose pH is at or below the pKa of lactic acid (3.78), allowing for the straightforward filtration of the acid form. Metabolic engineering has been used to create Lactobacillus sp. variations that are able to tolerate the acidified medium produced during fermentation. Following UV and nitrosoguanidine treatment, improved strains have been obtained, and they are now able to make lactic acid at rates and yields comparable to those of the conventional, neutral-pH lactic acid methods [97].

5. Importance of Probiotics for Mental Health

Probiotics are living microorganisms that are thought to gain health benefits when ingested. They are commonly found in certain foods such as yoghurt, kimchi, sauerkraut, and kefir. An emerging interest in the role of probiotics on mental health has been a burning topic recently. Studies have proposed the positive effect of probiotics on mental health via reducing inflammation, regulating the gut microbiota, and boosting stress response (Table 3). There is evidence to suggest that probiotics may help reduce symptoms of depression and anxiety, minimize stress-associated eating conduct, and improve cognitive outcomes [98]. Probiotics may help improve sleep quality, reduce fatigue, and boost mood. Furthermore, while more research work is necessary to better acknowledge the mechanisms and effects of probiotics on mental health, current evidence suggests that probiotics may be beneficial for overall mental health. It has been observed that the microbiota residing in the gastrointestinal tract (GIT) show an effect on the synaptic or neural signals produced by the CNS [99]. The term gut-brain axis depicts the association between the gut microbiota and the CNS. This association describes a relationship of the gut whose basis of communication is performed through the endocrine system, inflammatory responses, neural system, etc. Several researchers performed clinical trials to clarify this mutual association and have shown that a nerve, namely the vagus nerve, is responsible for the maintenance of the microbiota–gut-brain axis and performs a significant function in neurotransmitter signalling. The microbiota–gut-brain axis is a two-way mechanism. The microbiota present in the gut potentially influence the cognitive functions performed by the brain, such as remembrance power, memory, creativity, and controlling the centre of emotions, feelings, and sensations [100]. A clinical trial of probiotics containing Lactobacillus spp. was performed on mice, which resulted in lowering their anxiety levels. Many types of research are ongoing to specify the role of probiotics in the body, especially in the neural system. Probiotics show a positive effect on the mental health of an organism, and they help in stress management, act as anti-depressants, and cure various diseases like Parkinson’s disease, AD, autism, etc. In current studies, it has been found that the diet crucially contributes to the cognitive processes controlled by brain. The CNS involves the hypothalamic region that regulates stress and responds to stimuli. Dysfunction of the hypothalamic region or CNS can lead to neurodegenerative disorders [101].

Table 3. Different probiotic strains with their effect on neurological disorder.

<table>
<thead>
<tr>
<th>Neurological Disorder</th>
<th>Probiotics Strain</th>
<th>Mechanism</th>
<th>Reference/Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism spectrum disorder</td>
<td>Lactobacillaceae reuteri</td>
<td>It improves the neurotransmission and decreases the level of corticosterone.</td>
<td>[102]</td>
</tr>
<tr>
<td></td>
<td>Bifidobacterium fragilis</td>
<td>It restores the gut microbiota and improves gut permeability and physiology.</td>
<td>[103,104]</td>
</tr>
</tbody>
</table>
Table 3. Cont.

<table>
<thead>
<tr>
<th>Neurological Disorder</th>
<th>Probiotics Strain</th>
<th>Mechanism</th>
<th>Reference/Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress and depression</td>
<td><em>B. infantis</em></td>
<td>It has been seen that in the rat the treatment of <em>B. infantis</em> normalized the immune response and norepinephrine level in the brainstem.</td>
<td>[105]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td><em>L. rhamnosus GG, L. acidophilus, and Bifidobacterium animalis subsp. lactis</em></td>
<td>It increases the level of butyrate and the levels of BDNF and GDNF, which induces the survival of the neuronal cell and the synthesis of dopamine.</td>
<td>[106,107]</td>
</tr>
<tr>
<td>Reducing stress and enhancing memory</td>
<td><em>Bifidobacterium longum (B. longum) 1714</em></td>
<td>It induces an anti-stress response that helps in the reduction in stress.</td>
<td>[108,109]</td>
</tr>
</tbody>
</table>

6. Aetiology of AD

Around the world, the chronic neurological condition AD (AD) accounts for about 80% of all cases of dementia, mainly in persons over 60 years of age. In accordance with a thorough investigation for the Global Burden of Disease study, in the year 2016, about 43.8 million people worldwide were affected by AD. It is expected that by the year 2050, around 131 million people worldwide will be suffering from AD, constituting it as one of the biggest worldwide health and hygiene challenges of the upcoming future generation. Significant memory, cognitive, and motor deficits are hallmarks of AD [110]. This is primarily caused by the deposition of beta-amyloid plaque protein outside the neuron or the existence of tau tangles inside the neurons. This may change the calcium balance and cause neuroinflammation, vascular degeneration, and ultimately neuronal death. AD is tightly linked to neuron loss, synaptic dysfunction, and neurolip threads. Amyloid precursor protein (APP), a crucial component involved in the system for digesting proteins, is strongly associated with the aetiology of AD [111]. The noteworthy factors contributing to the prior development of AD include transmutations in the presenilin 1 (PSEN1) and presenilin (PSEN 2) proteins and APP. A delayed start in AD is caused due to a variety of factors involving lifestyle, ageing, food, environment, and overexpression of the apolipoprotein (Apo) E4 gene. In AD, beta-amyloid accumulation is prevalent. Beta-amyloid is a peptide produced when APP is cleaved by a proteolytic enzyme. By clathrin-mediated endocytosis, amyloid precursor protein derived from trans-Golgi networks is delivered into the endosomal compartment. A portion of the APP is recycled back to the surface of the cell during this process in the endosome [112]. A non-amyloidogenic route controls APP on the cell surface and -secretase functions at N-terminal terminus in the A domain. These produce 83 membrane-tethered amino acids with the carboxy-terminal ends and APP as a result (CTF). As a result, -secretase will continue to cleave CTF-83 to produce the living intracellular domain of P3 fragment and APP [113].

In the endosomal compartment, the APP will take the amyloidogenic pathway. A non-amyloidogenic route controls APP on the cell surface and secretase functions on the N-terminal terminus in the A domain. It produces 83 membrane-tethered amino acids with carboxy terminal ends and APP as a result (CTF). As a result, -secretase will continue to cleave CTF-83 to produce the functional intracellular domain of P3 fragment and APP [113]. The APP will take the amyloidogenic pathway in the endosomal compartment. In this route, the -secretase binds with the APP’s extracellular domain, resulting in 99 membrane-bound amino acids made up of APP and CTF-(C99). To create soluble A fragment and the APP intracellular domain, -secretase will further cleave C99 [114]. In the presence of transition metal ions like Fe$^{2+}$ and Cu$^{2+}$, which create H$_2$O$_2$, the A peptide oligomerizes. By promoting lipid peroxidation, this will eventually lead to the formation of 4-hydroxynonenal (4HNE). In contrast, impaired glucose and glutamate transport effects in an expansion in inositol 1,4,5-triphosphate (IP3) production and Ca$^{2+}$ influx led to the efflux of Ca$^{2+}$ from the storage of the endoplasmic reticulum. When calpain, which is calcium-dependent, becomes activated, CDK5 is induced, which leads to tau hyperphosphorylation, neurofibrillary tangle development, impairment of axonal transport, and microtubule
disassembly. In the end, it results in neuronal death and synaptic dysfunction [115]. The reactive oxygen species (ROS) and the increased inflow for Ca\(^{2+}\) ions into the mitochondria drive the production of mitochondrial cyclophilin D. As a result, proapoptotic substances such as apoptosis-inducing factor (AIF) and cytochrome C are released. An activation of the caspase cascade eventually causes the death of neuronal cells. Moreover, plaques cause a release of certain cytokines like IL-1, TNF, and IL-6 as well as a few chemokines like macrophage inflammatory protein-1 and IL8 from microglial cells. All of these in turn trigger the astrocytes’ production of acute-phase proteins, cytokines, and chemokines, which activates the microglial cells. The pathophysiology of AD is neuroinflammation, which is produced in the brain by activated astrocytes and microglia [116]. According to recent research, AD patients have an elevated concentration of immune cells that are peripheral, and these cells actively contribute to regional irritation. The pro-inflammatory cytokinin cells can penetrate through the blood–brain barrier (BBB) and furthermore incite some inflammatory responses like heat, soreness, and redness, which are particular to the brain but are nonetheless sources for peripheral inflammation, whether through obesity or systemic inflammation. As a result, the BBB becomes more permeable and porous, allowing peripheral immune cells to enter. Microglial cells will then become overactive. This will at first manifest in AD patients as reduced hippocampal-dependent learning [117].

7. Significance of Probiotics in Curing AD

Probiotics work through a wide range of processes depicted in Figure 4, albeit the precise way they do so is still not fully understood.

![Figure 4](image_url)

Various probiotic strains that are helpful in curing AD are mentioned in Table 4 below, which gives information regarding different probiotic strain and their effects in AD along with the mechanism.
Table 4. Different probiotic strains and their effects on AD with mechanisms of actions.

<table>
<thead>
<tr>
<th>Probiotic Strain</th>
<th>Effects on AD</th>
<th>Mechanisms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillaceae acidophilus</em></td>
<td>Improved cognitive function, reduced neuroinflammation, and enhanced amyloid clearance</td>
<td>Modulation of gut-brain axis, anti-inflammatory effects, and interaction with amyloid proteins</td>
<td>[118,119]</td>
</tr>
<tr>
<td><em>Bifidobacterium longum</em></td>
<td>Enhanced memory, reduced amyloid plaques, and attenuated neuroinflammation</td>
<td>Modulation of immune response, reduction in oxidative stress, and interaction with amyloid proteins.</td>
<td>[118,120]</td>
</tr>
<tr>
<td><em>Lactobacillaceae plantarium</em></td>
<td>Protection against cognitive decline, reduced neuroinflammation, and improved synaptic function</td>
<td>Regulation of neurotransmitters and anti-inflammatory effects and maintenance of blood–brain barrier integrity</td>
<td>[121,122]</td>
</tr>
<tr>
<td><em>Lactobacillaceae helveticus</em></td>
<td>Reduced cognitive decline, decreased amyloid accumulation, and attenuated neuroinflammation</td>
<td>Stress reduction, anti-inflammatory effects, and promotion of neuronal growth and connectivity.</td>
<td>[120,123]</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em></td>
<td>Protection against cognitive decline, reduced neuroinflammation, and improved neurogenesis</td>
<td>Regulation of gut permeability, anti-inflammatory effects, and modulation of immune response.</td>
<td>[124,125]</td>
</tr>
</tbody>
</table>

The creation of short-chain fatty acids, bacteriocins, modulation, the struggle for nutrition, and the stimulation of the gut-brain axis’s function are all examples of how this happens. Figure 5 illustrates a probiotic’s potential mode of action in AD in relation to this. Based on the amount of fibre in the diet, the formation of short-chain fatty acids (SCFAs), which are generally saturated fatty acids, takes place in the gut. The fermentation process, which is mediated by the microbial species *Lactobacillaceae*, *Clostridium*, *Bacteroides*, *Eubacterium*, and *Bifidobacterium*, produces the metabolites acetate, butyrate, and propionate [126]. Three key mechanisms—neuronal routes, immune modulation, and endocrine factors—may all play a role in how SCFAs affect brain function. By enhancing barrier integrity and maintaining mucus production through immunological regulation, SCFAs can affect intestinal mucosa susceptibility and barrier function. SCFAs influence the release of cytokines, which influences the immune cells’ ability to proliferate and differentiate [127]. Because of this association, pro-inflammatory cytokines (such as IL-1, TNF, and IL-6) are suppressed, whereas an anti-inflammatory reaction is produced. Moreover, the expression of tight junction proteins is increased, and short SCFAs could impact the integrity of the BBB and traverse BBB using monocarboxylate transporters. By altering the function and form of neural microglia cells in the CNS, SCFAs have an impact on neuroinflammation, avoiding the death of neuronal cells. The ejection of gut hormones is modulated by SCFAs, which function as endocrine signalling molecules. SCFAs improve boundary strength and preserve mucus through immunological regulation. Propionate and acetate greatly increase the production of PYY and glucagon-like peptide-1 (GLP-1) in mouse colonic cells by activating the G-protein-coupled receptor. Neurons and intestinal enteroendocrine L-cells in the nucleus of the brainstem of the tractus solitarius generate and secrete GLP-1 [128]. Glucagon-like peptide-1 functions in preventing cell death and neuronal apoptosis and as a neuroprotective agent in the brain. PYY serves as a gut hormone that reduces appetite. Studies on animals have shown that the neuropeptide Y is highly raised in the hippocampus, which is part of the temporal lobe, of mice with AD and has neuroprotective effects by activating the PI3K-XBP1-induced Gip78/BiP path as well as hindering caspase-4 and caspase-3 actions. It also reduces oxidative stress by preventing the Aβ-induced lipid peroxidation that causes modifications at the level of the neurotransmitter glutamate and oxidative stress [129].

Furthermore, neurotransmitters and neurotrophic factors may be modulated by short-chain fatty acids SCFAs. Investigations have shown that the gut microbiota can either create antecedents for neurotransmitters or catalyse their production and distribution through food consumption or even both [129]. Via secretory enterochromaffin (EC) cells, neurotransmitter precursors encourage the release of some neurotransmitters like GABA and 5-HT. Butyrate as well as propionate influences the production of 5-HT host from the serum and colonic endoplasmic reticulum, according to the findings of [130]. Cells of the EC generate several neuroactive by-products such as tryptophan, peptide tyrosine tyrosine
(PYY), and histamine. Certain neuroactive metabolites and precursors of neurotransmitters can penetrate through the blood–brain barrier (BBB) and participate in signalling in the CNS and in the brain, where neurotransmitter production takes place. Evident types of gut bacteria directly affect the signalling of the vagus nerve by stimulating the dorsal motor nucleus of the vagus nerve (DMV). An expanding body of evidence points to lengthy stress as a high-risk factor in the development of AD, which may quicken the progression of the disease. Stress and anxiety have a strong link to dementia risk [131,132]. Stress originating from outside or from the environment could cause psychological distress, which can be made worse by oxidative damage and inflammation. In response to psychological stress, the hypothalamic–pituitary–adrenal axis (HPA) is stimulated, which results in the discharge of glucocorticoids into the blood system and their passage through the blood–brain barrier into the brain for the activation of nutrient corticosteroid receptors in the mouse model and glucocorticoid receptors in humans, including both [133]. By reducing the hypothalamic–pituitary–adrenal axis’s hyperactivity that results from inflammatory processes and gut microbiota dysbiosis, probiotics have a pragmatic outcome on the microbiota–gut-brain axis. According to research by Mindus et al. [134] on the various Lactobacillus strains, Lactobacillaceae rhamnoses, a probiotic, reduced anxiety-like behaviour and decreased corticosterone levels in non-stressed mice. It is currently thought that stress and HPA dysregulation are related, but the precise mechanism is still unknown. In the case of a mouse model with ongoing anxiety and stress brought on via maternal separation, a probiotic, namely Bifidobacterium pseudocatenulatum, enhanced glucocorticoid responsiveness and reduced inflammation induced by stress [131]. By restoring the brain expression levels of important glucose transporters (GLUT3 and GLUT1) and insulin-like growth factor receptor along with the diminished phosphorylation of adenosine-monophosphate-activated protein kinase and protein-kinase B (Akt), the study showed that oral administration of probiotics improves glucose uptake in 3xTg-AD mice. Parallel to this, mice treated by Bonfili et al. [135] showed a reduction in phosphorylated tau clumps. In line with memory enhancement, probiotics prevent the time-dependent rise in glycated haemoglobin and the build-up of advanced glycation end products in AD mice.

![Figure 5. The microbiome–gut-brain axis in AD.](image)

There were 35 total research studies carried out by Ji and Shen [136] including 26 studies using animal models and 9 studies using humans. In the 26 animal model studies, mice were employed in 24 of them, whereas AD models from Caenorhabditis elegans and
Drosophila melanogaster were used in two of them, respectively. Thirteen studies used single-strain probiotics, while the remaining studies used multi-strain probiotics (ranging from two to nine probiotic strains); four used probiotic-fermented milk or probiotic-fermented soybean; two studies used engineered probiotic strains; and four studies concentrated on the synergistic effect of probiotics with the AD drug memantine, selenium, or exercise. The most often used probiotics in the trials that were included were Bifidobacterium and Lactobacillaceae species. These investigations demonstrated that probiotic treatment had neuroprotective effects, could lessen cognitive impairments, and could control gut microbiota dysbiosis, which may be connected to oxidative and inflammatory pathways. Probiotics appear to be an appealing strategy to treat AD, which opens the door for further study through carefully planned, large-scale clinical research. The effectiveness and safety of Lactobacillaceae plantarum C29-fermented soybean (DW2009) as a dietary supplement for improving cognition were examined by Hwang et al. [137]. For 12 weeks, 100 people with mild cognitive impairment (MCI) were randomly assigned to receive either DW2009 (800 mg/day, \( n = 50 \)) or a placebo (800 mg/day, \( n = 50 \)). The change in the composite score of memory- and attention-related cognitive abilities as determined by computerised neurocognitive function assessments served as the major outcome measure. For every single therapy group, correlations between changes in serum brain-derived neurotrophic factor (BDNF) levels and cognitive function were assessed. The DW2009 group had larger gains in the total cognitive functions as opposed to the placebo group (\( z = 2.36, p \) for interaction = 0.02), particularly in the attention domain (\( z = 2.34, p \) for interaction = 0.02). Following ingestion of DW2009, elevated blood BDNF levels were linked to improved cognition (\( t = 2.83, p = 0.007 \)). The outcomes of this clinical research indicate that DW2009 can be provided without risk to MCI patients to improve their cognitive abilities. Increased serum BDNF levels after DW2009 administration may offer a glimpse into the mechanisms driving cognitive recovery, which supports the role of the gut-brain axis in treating MCI’s cognitive abnormalities [137].

8. Probiotics Safety Considerations

In accordance with the American Food and Drug Administration (FDA), probiotics are considered safe. The efficacy of Lactobacillaceae, Bifidobacterium, Clostridium, and Streptococcus species in AD has not yet been subject to any recorded data. Probiotics should not always be given to patients with ongoing AD, especially the ones who are accepting drugs that act as immunosuppressors, such as chemotherapy [138]. Many incidences of fungemia, bacteraemia, and sepsis demonstrated in people who received S. boulardii have been documented. Probiotic bacteria might occasionally include genes for antibiotic resistivity, which can be passed on to additional another bacterium, to potentially pathogenic strains that can lead to infection. Probiotic safety should consider the characteristics of the probiotic, the patient/consumer, and the manufacturing process. (Contaminated probiotics products represent a safety concern). While some can be determined right away, others require more research before any meaningful recommendations can be made [139].

9. Conclusions

Disorders of the twenty-first century, including obesity, anxiety, depression, Parkinson’s disease, diabetes, and AD, may seem to have completely different aetiologies, yet they have a few similarities, as they are all non-communicable, non-transmissible illnesses or disorders for which there is now no effective treatment to completely cure their symptoms. A wealth of literature connects these illnesses to changes in the microbiota. It has been demonstrated that several probiotics improve microbiome stability, which has positive effects on brain health and is especially helpful in preventing neurodegenerative diseases like AD. In summary, this review offers a wealth of research that is supported by evidence regarding the contribution of probiotics to slowing the progression of AD. Clinical trials and in vivo research have demonstrated the value of probiotics in the therapeutic arena for the treatment of AD. According to this claim, there have been no negative effects concerned
with the consumption of probiotics for AD. For the sake of identifying changes in the gut microbiome that are specific to AD and that might further reveal new information about probiotics as an excellent curative source in the future, more clinical trials must be carried out. Furthermore, extensive research linking cognitive function with microbial diversity and the development of disease in AD patients might yield useful, predictive information.

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