

***Lactobacillus Plantarum* for Human Life: Molecular Approach**

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Abstract

Lactobacillus plantarum (L. plantarum) increases short-chain fatty acids (SCFA) levels in the intestines, which acts as a signal to activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. This activation is crucial for reducing oxidative stress and maintaining mitochondrial balance. This study aims to review several research papers that explore and highlight how *L. plantarum* makes SCFAs to activate Nrf2, specifically the strategies it uses to combat free radicals. The systematic review technique systematically investigates, assesses, analyzes, and interprets all study findings relevant to the research topic. We sourced articles from three databases: Scopus, Web of Science, and Google Scholar, covering the period from 2014 to 2024. The study found that SCFAs made by *L. plantarum* are important signals that trigger the Nrf2 signaling pathway, which helps protect cells from damage caused by oxidation and inflammation. *L. plantarum* is a beneficial probiotic that uses SCFAs to trigger the Nrf2 pathway, providing strong protection against free radicals and supporting various health benefits.

Keywords: *Lactobacillus plantarum*, SCFA, Nrf2, free radicals, and probiotic.

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Introduction

L. plantarum is a multifaceted lactic acid bacterium with considerable applications in the food and health industries. It is frequently located in diverse habitats, encompassing food products and the mucosal surfaces of people and animals (Mayo & Flórez, 2022). This bacterium is recognized for its capacity to ferment various carbohydrates, generating lactic acid as a principal metabolite; hence it improves

fermented goods' sensory attributes and shelf stability. *L. plantarum* is acknowledged for its probiotic attributes, offering health advantages including enhanced gastrointestinal health, metabolic management, and cardiovascular protection (Corsetti & Valmorri, 2011). *L. plantarum* is commonly used as a starter culture to ferment dairy, meat, fish, and vegetables, which helps make these foods better in quality and safer to eat. The bacterium's capacity to synthesize beneficial chemicals such as bacteriocins extends the shelf life of food products by suppressing detrimental microorganisms (Behera et al., 2018). *L. plantarum* influences the gut microbiota and diminishes local inflammation, enhancing gastrointestinal health (Soto et al., 2024). It facilitates glucose and lipid metabolism, providing possible advantages for individuals with diabetes and obesity (Soto et al., 2024). The bacterium has shown it can reduce plaque buildup in arteries and improve blood vessel function, suggesting it may help prevent heart diseases (Soto et al., 2024). *L. plantarum* is used to develop functional meals with enhanced nutritional and technical attributes, including increased antioxidant activity and antibacterial capabilities (Behera et al., 2018; Zare et al., 2024).

L. plantarum increases the levels of SCFA in the intestines, which act as signals to turn on the Nrf2 pathway, helping to reduce oxidative stress and maintain balance in mitochondria (Li et al., 2024a). When *L. plantarum* activates Nrf2, it increases the levels of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, which are crucial for combating free radicals. *L. plantarum* J26 helps treat liver disease, decreases fat accumulation, and supports mitochondria in the liver when it's damaged by alcohol by activating Nrf2. Nrf2 can be activated by various factors, including molecular hydrogen (H₂), which enhances its antioxidant capabilities. This activation of Nrf2 causes the body to make important antioxidant enzymes, such as catalase, glutathione, and superoxide dismutase, which help fight off harmful free radicals (Xie et al., 2022). *L. plantarum* FC225 has been shown to lower harmful fat levels and increase the activity of antioxidant enzymes in mice with high fat levels, highlighting its potential for treating fat-related diseases. In studies on aging, *L. plantarum* AR501 boosts the production of antioxidant genes controlled by Nrf2, which helps reduce oxidative stress and liver damage (Chen et al., 2022).

Nrf2 is a key protein that helps the body fight oxidative stress and inflammation (Wang et al., 2022). *L. plantarum*, a helpful bacterium, makes SCFAs that activate the Nrf2 signaling pathway, which protects our cells from harm. This activation results in the production of antioxidant genes, thereby alleviating oxidative stress. Short-chain fatty acids act as signals that help move Nrf2, a protein that controls the output of genes related to the body's defense against damage from free radicals (Aboulgheit et al., 2021). This activity is crucial for sustaining cellular homeostasis and safeguarding against oxidative damage. Short-chain fatty acids made by *L. plantarum* can activate the Nrf2 signaling pathway, which is important for reducing oxidative stress in liver cells. This activation helps keep mitochondria healthy and reduces cell death, which helps reduce liver damage caused by alcohol (Li et al., 2024a). In microglial cells, compounds from *L. plantarum* increase Nrf2 activity in the nucleus, resulting in increased production of antioxidant genes like heme oxygenase 1 and superoxide dismutase (SOD). According to Di Chiano et al. (2024) the activation of Nrf2 by *L. plantarum* results in the production of more antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, which are essential for protecting the body from harmful reactive oxygen species (Mu et al., 2019). In addition to antioxidant enzymes, genes like glutathione-S transferase and catalase increase, strengthening the body's ability to fight against oxidative stress (Gao et al., 2013). *L. plantarum* might change dietary phenolic acids into strong Nrf2 activators like 4-vinylcatechol, which helps turn on Nrf2 target genes and boosts the body's antioxidant response.

L. plantarum, a helpful probiotic, has been widely studied for its health benefits, particularly related to SCFAs, the Nrf2 pathway, and its ability to fight free radicals. Previous studies have shown that *L. plantarum* can help protect against damage from oxidative stress and inflammation, usually through the Nrf2 pathway. This bacterium's capacity to regulate gut microbiota and synthesize bioactive chemicals amplifies its medicinal potential. A study by Rezgui et al. (2023) showed that substances made by *L. plantarum* help protect HepG2 cells from damage caused by hydrogen peroxide (H₂O₂). The ability of this protection mostly relies on the Nrf2 pathway, since stopping Nrf2 weakens the protective effects of *L. plantarum* substances. When Nrf2 is turned on, it boosts the production of protective enzymes that lower damage from oxidation and inflammation, which is indicated by reduced levels of TNF- α and IL-6 in the treated cells. *L. plantarum* demonstrates considerable free radical scavenging activity, enhancing its antioxidant capabilities. This function is essential for mitigating oxidative stress, a prevalent contributor to numerous disorders (Rezgui et al., 2023; Zhao et al., 2023). *L. plantarum* converts hydroxycinnamic acids into phenylpropionic acid, which works better as an antioxidant, showing how it helps lower oxidative stress (Chen et al., 2022). *L. plantarum* is recognized for its ability to alter the gut microbiota, resulting in the formation of SCFAs. These fatty acids are crucial for preserving gut health and exhibit systemic effects, including anti-inflammatory characteristics (Ngo & Duennwald, 2022). Probiotics can stick to the gut lining and survive tough conditions, which helps them improve gut health and produce SCFAs. *L. plantarum* is linked to several health benefits, such as boosting the immune system, lowering inflammation, and potentially helping with metabolic diseases and stress-related problems, in addition to its antioxidant and gut health advantages. *L. plantarum* has shown great success in reducing blood sugar levels and improving metabolic health in animal studies, suggesting it could help manage diabetes (Huang et al., 2019). So far, no detailed review has looked at how *L. plantarum* produces SCFAs and activates Nrf2, particularly in relation to fighting free radicals. This study aims to reviews several research papers that explore and highlight how *L. plantarum* makes SCFAs to activate Nrf2, specifically the strategies it uses to combat free radicals. This study attempts to answer the research questions (Table 1).

Table 1. Research questions

Code	Research question	Objective
RQ1	What is the role of <i>L. plantarum</i> in the food and health industry?	To analyze articles related to the role of <i>L. plantarum</i> in the food and health industry
RQ2	In what ways does <i>L. plantarum</i> promote health by producing SCFAs that activate the Nrf2 signaling pathway and enhance antioxidant gene expression?	To analyze articles related to <i>L. plantarum</i> promote health by producing SCFAs that activate the Nrf2 signaling pathway and enhance antioxidant gene expression
RQ3	How do SCFAs from <i>L. plantarum</i> molecularly activate Nrf2 and trigger antioxidant gene expression in host cells?	To identify articles related to the SCFAs from <i>L. plantarum</i> molecularly activate Nrf2 and trigger antioxidant gene expression in host cells

Methods

This research employs a method that includes procedures, analysis, and data synthesis.

2. 1 Procedure

We conducted this study using a systematic review method, a structured and methodical approach to synthesizing existing research on a particular topic. The goal is to analyze, explore, and interpret all research findings related to the research question (Visic, 2022; Angioi & Hiller, 2023). This study began by formulating three research questions (Table 1). The procedure includes searching for relevant articles, evaluating and screening, selecting potential articles through PRISMA diagrams, qualitative assessment and synthesis of results, and finally writing the research report. We searched for relevant papers in three databases: Web of Science, Scopus, and Google Scholar. We selected papers from 2016 to 2024 to compile the latest findings (Figure 1). Figure 1 illustrates the annual distribution of gathered articles. The annual publication of articles rises, reaching its zenith in 2024, with the exception of 2021. The search and compilation of publications in the Web of Science, Google Scholar, and Scopus databases yielded 781 items. The quantity of papers published from 2016 to 2024 is as follows: 42, 65, 67, 89, 93, 82, 98, 118, and 127. We conducted a literature search using the keywords *Lactobacillus plantarum*, SCFA, Nrf2, free radicals, and probiotic.

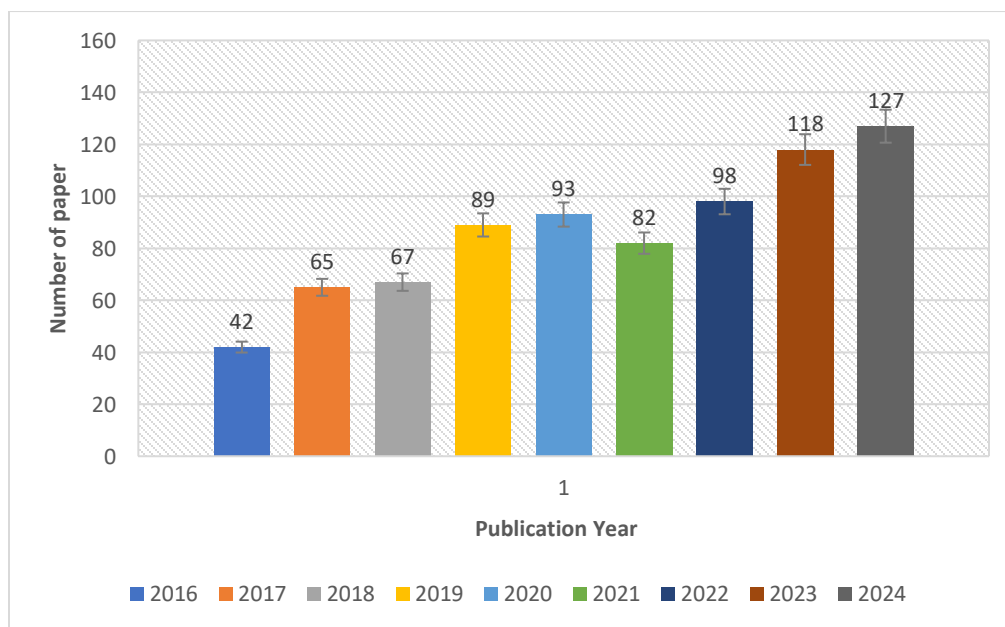


Figure 1. The number of papers published from 2016 to 2024

2.2 Analysis

We collected papers from 3 databases, namely Scopus (321 papers), Web of Science (232 papers), and Google Scholar (228 papers) (Figure 2).

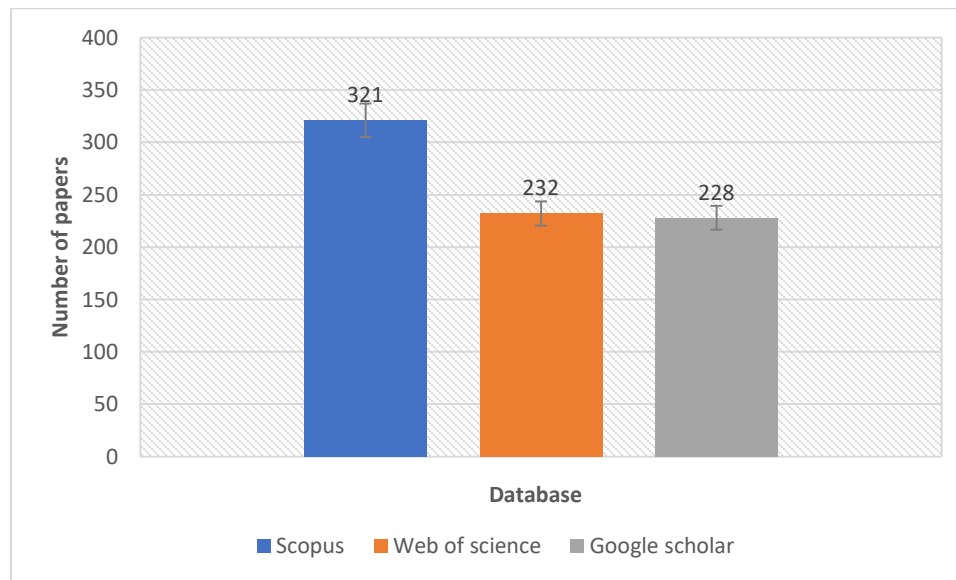


Figure 2. The number of papers categorized by database.

We looked at potential papers using the PRISMA flowchart (Figure 3) created by Haddaway et al. (2022). Figure 3 illustrates the potential articles obtained through the identification, screening, and inclusion stages. During the identification stage, 93 papers were identified as duplicates, 121 were deemed ineligible, and 87 were excluded for various reasons, resulting in 480 papers that progressed to the screening phase. In the screening stage, we eliminated 157 papers, did not retrieve 167 articles, and removed 133 reports for various reasons. During the inclusion stage, we merged additional research reports and selected a total of 23 potential articles for the literature review.

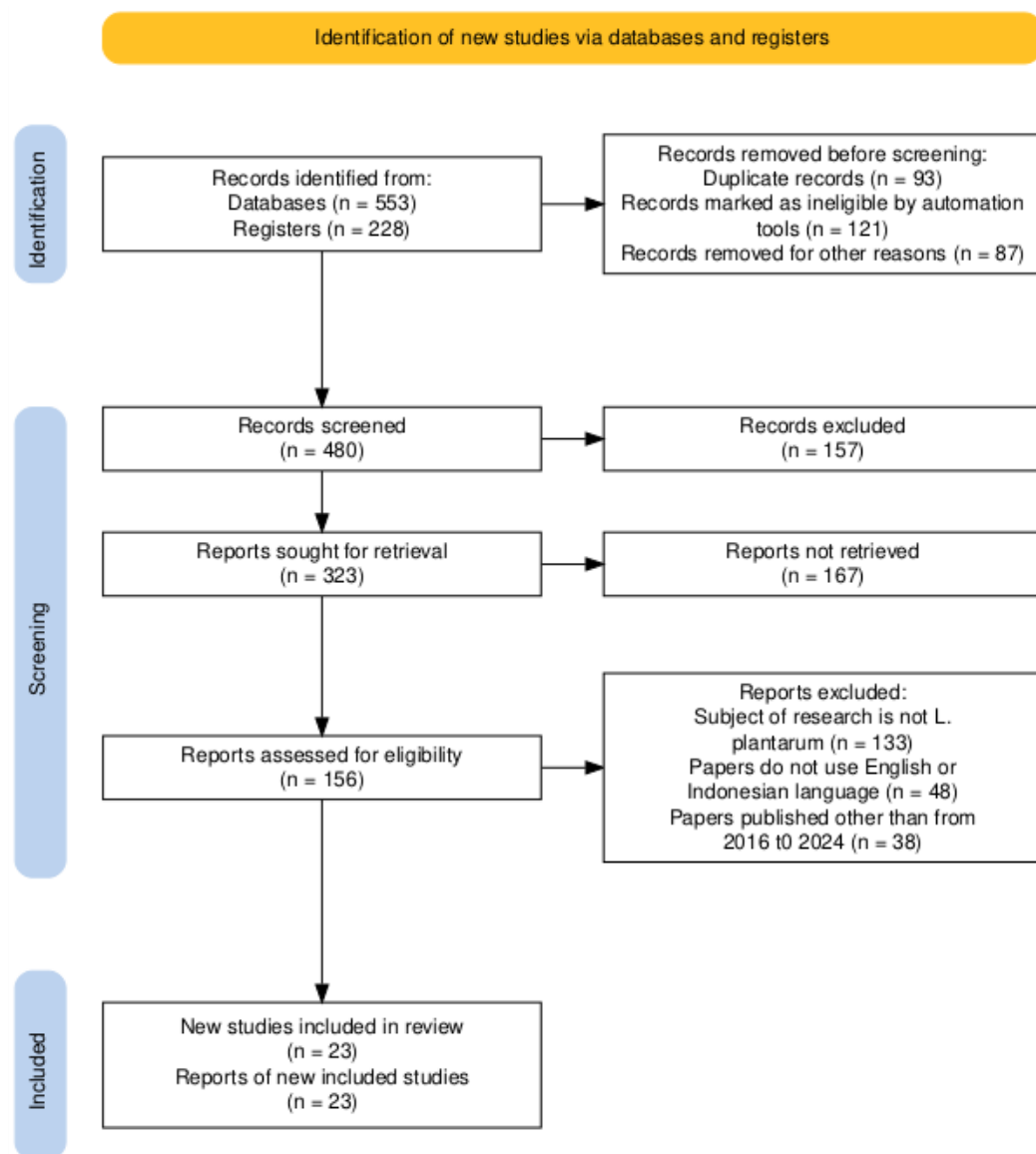


Figure 3. PRISMA flow diagram

Article selection was based on title, abstract, and full text according to inclusion and exclusion criteria (Table 2).

Table 2: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
The research subject studied is the role of <i>L. plantarum</i> as a free radical	The subject of the study did not examine the role of <i>L. plantarum</i> as a free radical
Articles are harvested from databases: Scopus, Web of Science, and Google Scholar	Articles are from the ResearchGate, Semantic, and Eric databases

Articles examine <i>L. plantarum</i> : SCFA, Nrf2, and molecular strategies against free radicals	Articles do not discuss <i>L. plantarum</i> : SCFA, Nrf2, and molecular strategies against free radicals
Articles published in the period 2016 to 2024	Articles published outside the period 2016 to 2024
Articles already have a digital object identifier (DOI)	Articles do not have a digital object identifier (DOI)
Investigation utilizing quantitative data derived from experimental outcomes	Investigations do not utilize quantitative data obtained from experimental results
Conduct research with quantitative methodologies, including descriptive surveys, experiments, or a combination of both.	Conducting research without quantitative methodology, including descriptive surveys, experiments, or a combination of both.

2.3 Data Synthesis

We conducted data synthesis on RQ1, RQ2, and RQ3 to compile the most recent findings. In light of the limited studies and the variety of study designs, we refrain from performing a quantitative meta-analysis. We opted for a narrative synthesis strategy, which systematically integrates all data from the selected studies. We evaluated 23 prospective papers according to the research questions: RQ1 included 9 articles, RQ2 included 8 articles, and RQ3 contained 6 articles (refer to Figure 4). We examined the 23 potential articles, encompassing the initial author, country of origin, results, and conclusions.

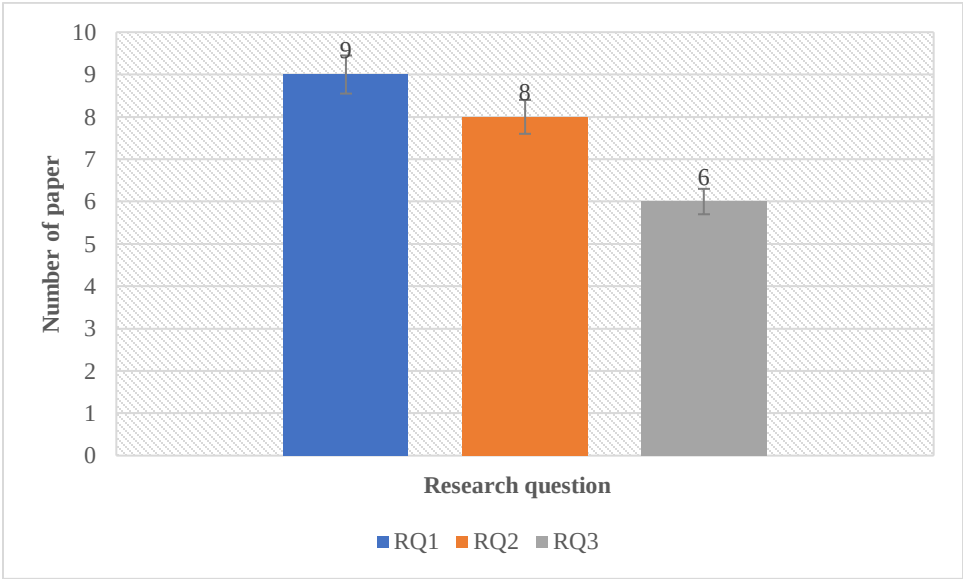


Figure 4. Number of papers based on RQ

Result and Discussion

We successfully conducted a systematic review of *L. plantarum*: SCFA, Nrf2, and molecular strategies against free radicals. This study successfully answered all the research questions designed previously.

RQ1: What is the role of *L. plantarum* in the food and health industry?

L. plantarum is a multifaceted bacterium with considerable applications in the food industry, mainly owing to its probiotic characteristics and capacity to improve food quality and safety (Table 3).

Table 3. The role of *L. plantarum* in the food and health industry

Author	Country	Result	Conclusion
Behera et al. (2018)	India	<i>L. plantarum</i> strains have strong probiotic qualities that can effectively fight harmful germs, including those that cause foodborne illnesses, which helps make fermented foods safer and last longer. These strains exhibit the capacity to produce antimicrobial chemicals and biosurfactants, which enhance their protective activities during food processing and storage.	<i>L. plantarum</i> strains, taken from locally fermented foods, are very effective at fighting different harmful bacteria, including both Gram-negative and Gram-positive types, which helps make fermented foods safer and last longer because of their ability to kill germs, prevent spoilage, and support gut health.
Yu et al. (2021)	USA	The research indicated that <i>L. plantarum</i> strains derived from analogous plant food sources demonstrate similar carbohydrate metabolism and stress tolerance responses, with strains from acidic, brine-rich ferments (such as olives and tomatoes) exhibiting enhanced resistance to low pH and high salinity conditions in contrast to those from grain fermentations. Olive-associated strains exhibited vigorous growth on raffinose and greater ethanol tolerance compared to the majority of other isolates.	The study finds that <i>L. plantarum</i> shows a lot of differences within its species, with strains from similar plant foods having comparable ways of processing carbohydrates and handling stress, especially highlighting that strains from acidic, salty ferments like olives and tomatoes are more resilient than those from grain ferments.

Zare et al. (2024)	Iran	The research describes <i>L. plantarum</i> as a versatile microorganism used in making food, highlighting its role as a starter culture in various fermentation processes that enhance the taste, smell, and texture of food. It also highlights the species' capacity to produce antimicrobial chemicals, which enhances the safety of the final product.	<i>L. plantarum</i> possesses numerous applications in the food sector, having been isolated from diverse food products including meat, fish, fruits, vegetables, milk, and cereal items. It functions as a starter culture in food fermentation, improving the organoleptic characteristics, flavor, and texture of the finished goods.
Dinev et al. (2018)	Bulgaria	<i>L. plantarum</i> is very effective at fighting off many harmful germs and spoilage organisms, including both types of bacteria (Gram-positive and Gram-negative) like <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , and <i>Listeria monocytogenes</i> , as well as molds and yeasts like <i>Aspergillus</i> and <i>Candida</i> spp. The antibacterial effect is ascribed to the synthesis of bacteriocins, organic acids, and other inhibitory compounds.	<i>L. plantarum</i> is recognized as an important type of lactic acid bacteria (LAB) that has strong antibacterial qualities, making it a good option for keeping food safe and for treating diseases caused by certain germs. The antimicrobial agents produced by <i>L. plantarum</i> , such as bacteriocins and organic acids, could serve as alternatives to traditional preservatives and treatments.
Silva et al. (2019)	Brazil	The research highlights the beneficial qualities of exopolysaccharides (EPS) produced by <i>L. plantarum</i> , pointing out their potential uses in the food industry, such as acting as gelling agents, emulsifiers, or stabilizers that improve the texture and consistency of food products.	EPS synthesized by <i>L. plantarum</i> has significant and advantageous qualities, especially regarding their rheological and prebiotic attributes, which are crucial for prospective industrial uses in food items.

Prete et al. (2020)	Italy	The research clearly described 22 <i>L. plantarum</i> strains related to food and the gut using multilocus sequence typing (MLST), finding six different lineages, which helps us understand the variety and possible uses of these strains in functional foods.	The research clearly identified 22 <i>L. plantarum</i> samples related to food and the gut using multilocus sequence typing (MLST), discovering six different lineages, which helps us see the variety and potential uses of these strains in functional foods.
Minj et al. (2021)	India	The research highlights the health benefits of probiotic Lactobacillus, showing that they can fight bacteria, reduce inflammation, act as antioxidants, and may help manage diseases like diabetes and cancer. The characteristics of Lactobacillus strains render them significant in the formulation of functional meals.	Using lactic acid bacteria, particularly Lactobacillus, as probiotics makes food more effective and provides many health benefits, such as fighting bacteria, reducing inflammation, and supporting the immune system, all of which are important for our health.
Liu et al. (2018)	Malaysia	<i>L. plantarum</i> strains are very helpful for health, particularly in reducing gut problems such as inflammatory bowel diseases (IBD), metabolic syndromes, high cholesterol, obesity, and diabetes, showing that they are effective probiotics for improving gut health and managing metabolism.	<i>L. plantarum</i> is recognized as a type of lactobacillus that does not remain stable in the human gut, but it still shows strong probiotic benefits and biological effects, highlighting that the specific qualities of each strain are more important than the general benefits that apply to all strains.
Zhang et al. (2021)	China	Drinking <i>L. plantarum</i> ZDY2013 fermented milk before or after getting infected with enterotoxigenic <i>Bacillus cereus</i> helped prevent weight loss and gut damage, returned	The study shows that <i>L. plantarum</i> ZDY2013 fermented milk effectively reduces the harmful effects caused by enterotoxigenic <i>Bacillus cereus</i> , such as damage to the intestines

inflammatory markers IL-1 β and IL-10 to normal levels, and resulted in lower platelet counts and uric acid levels.	and problems with bowel function, while also balancing gut bacteria. This is demonstrated by the restoration of body weight, histological architecture of the gastrointestinal tract, and serum concentrations of inflammatory markers.
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In Table 3 there are 9 articles published from 2018 to 2024 that examine the role of *L. plantarum* in the food and health industry. *L. plantarum* is widely used in making food, improving the taste, smell, and feel of many different products. Its applications include food preservation, the synthesis of bioactive substances, and serving as a starting culture in dairy and other fermented goods. *L. plantarum* is widely used as a starting culture in the fermentation of dairy products, vegetables, and grains. It facilitates the formation of favorable flavors and textures in these items (Zare et al., 2024; Todorov & Franco, 2010). The bacterium improves the flavor profile of fermented foods by generating diverse flavor molecules during fermentation. The process encompasses the synthesis of lactic acid and other metabolites that enhance the sensory characteristics of the final product (Du et al., 2023). *L. plantarum* has strong antibacterial properties because it produces bacteriocins and organic acids that stop harmful bacteria and spoilage organisms from growing. This property renders it an efficient biopreservative, prolonging the shelf life of food goods (Dinev et al., 2018).

The utilization of *L. plantarum* in food goods can markedly extend their shelf life. For example, its application in bread fermentation can prolong the shelf life from 5 to 14 days (Dinev et al., 2018). *L. plantarum* synthesizes exopolysaccharides that have technological and health advantages. These chemicals function as gelling agents, emulsifiers, or stabilizers in food items, enhancing their texture and stability (Silva et al., 2019). The ability of the bacterium to produce beneficial chemicals that fight free radicals improves the nutrition and health benefits of the foods it is added to (Silva et al., 2019). *L. plantarum* is acknowledged for its probiotic properties, which include the modulation of gut microbiota and the enhancement of immune responses. These attributes render it a significant element in functional foods designed to enhance gut health (Du et al., 2023). The microorganism is utilized to create novel functional foods and drinks that include enhanced nutritional and technological attributes, providing additional health advantages to customers (Behera et al., 2018).

L. plantarum, a multifaceted and extensively researched probiotic, exerts considerable effects on gastrointestinal health and the advancement of functional foods. Its probiotic qualities are shown by its ability to survive the journey through the stomach, settle in the intestines, and offer many health benefits, making it an important part of the food industry. The probiotic attributes of *L. plantarum* promote gut health by regulating gut microbiota, augmenting immune responses, and possibly averting gastrointestinal diseases. These characteristics make it a viable choice for the creation of functional foods intended to enhance health outcomes. *L. plantarum* can change the types of bacteria in the gut by increasing helpful bacteria like *Lactobacillus* and *Bifidobacterium* and reducing harmful bacteria like *Bacillus cereus*. This modulation aids in maintaining gut homeostasis and promotes overall gut health (Ismael et al., 2022); (Zhang et al., 2021). *L. plantarum* possesses probiotic qualities that include

immunological regulation, so it augments the body's resistance to infections and diminishes inflammation. This goal is accomplished by regulating cytokine production and immune cell function (Kaushik et al., 2009).

L. plantarum can lower cholesterol levels by breaking down bile salts and producing short-chain fatty acids (SCFAs), which are beneficial for heart health. *L. plantarum* is widely used in the fermentation of dairy, meat, and vegetable products, improving their nutritional quality and longevity. The capacity to generate bioactive chemicals, including bacteriocins, enhances the safety and preservation of fermented foods (Behera et al., 2018). Researchers are looking into how *L. plantarum* strains can be used to create functional foods that help with specific health issues, such as reducing the risk of heart disease and managing metabolic disorders (Wang et al., 2022). *L. plantarum* is utilized in various food products, such as yogurt, cheese, and fermented drinks, owing to its capacity to endure varying environmental conditions and its advantageous health impacts (Belicová et al., 2013). According to Behera et al. (2018), *L. plantarum* is commonly considered safe (GRAS) and possesses a qualified presumption of safety (QPS) designation. Research indicates that it lacks virulence factors and antibiotic resistance genes, rendering it a suitable option for probiotic applications (Liu et al., 2018); (Ismael et al., 2022). Different strains of *L. plantarum* have unique probiotic features, such as the ability to fight off harmful substances and bacteria, which can be used for specific health benefits and creating functional foods. The probiotic features of *L. plantarum* offer many benefits for gut health and creating functional foods (Minj et al., 2021). However, it's important to consider the differences between strains and the specific makeup of a person's gut microbiota. The effectiveness of *L. plantarum* as a probiotic can vary based on these traits, which illustrates the importance of personalized approaches when using probiotics. Additionally, more research will enhance the benefits of *L. plantarum* for health and nutrition by exploring how it works and interacts with the host's digestive system.

RQ2: In what ways does *L. plantarum* promote health by producing SCFAs that activate the Nrf2 signaling pathway and enhance antioxidant gene expression?

L. plantarum boosts health by making short-chain fatty acids (SCFAs), which activate the Nrf2 signaling pathway and raise antioxidant genes. This probiotic strain has shown it can reduce oxidative stress and boost antioxidant defenses in various situations, such as liver damage and aging (Table 4).

Table 4. *L. plantarum* promotes health through SCFA production that activates Nrf2 and antioxidant genes.

Author	Country	Result	Conclusion
Li et al. (2024)	China	<i>L. plantarum</i> J26 activated the Nrf2 signaling pathway, which increased the levels of antioxidant proteins like NQO1 and HO-1, helping to reduce oxidative stress and maintain healthy mitochondria, thereby reducing liver damage caused by alcohol.	The study showed that <i>L. plantarum</i> J26 raised the levels of short-chain fatty acids (SCFAs) in the intestines, which helps activate the Nrf2 signaling pathway. This activation reduces oxidative stress in the liver by boosting peroxidase activity, managing mitochondrial balance and cell recycling, and lowering liver cell

			death; as a result, it helps reduce liver damage caused by alcohol.
Gupta et al. (2024)	India	<i>L. plantarum</i> might influence how we age by changing the bacteria in our gut, which could improve issues related to aging, such as oxidative stress, inflammation, DNA methylation, and mitochondrial dysfunction.	Taking <i>L. plantarum</i> may help reduce aging and health risks by influencing signs of aging, such as oxidative stress, inflammation, DNA methylation, and mitochondrial dysfunction.
Aboulgheit et al. (2021)	Rhode Island	The probiotic strain <i>L. plantarum</i> can help the heart work better by triggering a protective process in cells that fight damage from stress.	The colonization of the gut microbiome by <i>L. plantarum</i> enhances the transformation of caffeic acid from applesauce into 4-vinyl-catechol, a molecule that serves as a robust activator of the Nrf2 antioxidant pathway, hence promoting cardiovascular health.
Wang et al. (2021)	China	The combination of <i>L. plantarum</i> 69-2 and galacto-oligosaccharides (GOS) significantly improved liver function and antioxidant activity while reducing inflammation in older mice, also changing gut bacteria and increasing short-chain fatty acid (SCFA) levels.	The research shows that <i>L. plantarum</i> 69-2 and GOS stimulate the liver's AMPK/SIRT1 signaling pathway, which increases the liver's antioxidant activity and helps lessen the effects of aging through the connection between the gut and liver, offering a new way to address aging by changing gut bacteria.
Zhao et al. (2019)	China	<i>L. plantarum</i> NA136 turned on the AMPK pathway, which caused ACC to be modified, stopping the SREBP-1/FAS signaling and lowering the production of new fats while boosting the breakdown of fatty acids. It also helps Nrf2 move into the nucleus, activating the antioxidant pathway to reduce oxidative stress. Additionally, it helped move Nrf2 into the nucleus,	The way it works involves activating the AMPK pathway, which leads to the phosphorylation of ACC, blocking SREBP-1/FAS signaling to reduce new fat production, and increasing fatty acid breakdown, while also boosting the movement of Nrf2 into the nucleus to start antioxidant processes

		which activated the antioxidant pathway to reduce oxidative stress.	that help reduce oxidative stress.
Rezaie et al. (2024)	Iran	Lactobacillus strains help protect against metabolic disorders by increasing the levels of short-chain fatty acids (SCFAs), particularly acetic acid in stool, and improving gut bacteria imbalances, which helps adjust the microbiota and raise acetate levels.	Lactobacillus strains help correct imbalances in gut bacteria and provide some protection against metabolic syndrome caused by diet; however, they do not fully return the bacteria to a normal state, indicating that the recovery is only partial.
Senger et al. (2016)	USA	The research identified alkyl catechols, namely 4-methylcatechol, 4-vinylcatechol, and 4-ethylcatechol, as effective co-factors for the activation of the Nrf2 cellular defense pathway, significantly enhancing the expression of Nrf2 target genes across diverse human cell types both in vitro and in vivo. Significantly, 4-ethylcatechol demonstrated oral bioactivity in mice.	The research shows that alkyl catechols are useful natural helpers for turning on the Nrf2 cellular defense system, proving to work well in both lab tests and living organisms. The chemicals 4-methylcatechol, 4-vinylcatechol, and 4-ethylcatechol have been shown to increase the activity of Nrf2 target genes in different human cell types, highlighting their role in strengthening the cell's defense against oxidative stress.
You et al. (2023)	China	<i>L. plantarum</i> P101 improves the body's ability to fight damage from free radicals by activating the Nrf2/ARE signaling pathway, which helps protect the liver and reduce liver cell death in mice given cyclophosphamide.	<i>L. plantarum</i> P101 improved the body's antioxidant defense by activating the Nrf2/ARE signaling pathway, which helped reduce liver damage and lower liver cell death in mice treated with cyclophosphamide

According to Table 4, *L. plantarum* promotes health by producing SCFAs that activate the Nrf2 signaling pathway and antioxidant genes. *L. plantarum*, a probiotic bacterium, modulates the gut microbiota, thus impacting SCFA. These SCFAs are essential in regulating liver function and alleviating age-related hepatic damage (Wang et al., 2022). The connection between *L. plantarum* and SCFAs mainly happens through the gut-liver axis, which includes complicated metabolic processes and signaling methods. Strains of *Lactobacillus plantarum*, like *L. plantarum* 69-2, can increase SCFA levels by

changing the type of bacteria in the gut. This change is important because it activates the AMPK/SIRT1 signaling pathway in the liver, which helps the liver work better and protects itself from damage, reducing the effects of aging (Sun et al., 2023). The injection of *L. plantarum* TY-Y10 in older mice increased the number of bacteria that produce SCFAs, which in turn raised the levels of SCFAs in their feces. The elevation of SCFAs is correlated with less oxidative stress and enhanced liver health (Li et al., 2024a). *L. plantarum* NKK20 was shown to raise SCFA levels in the colon, which helped lessen inflammation and liver harm in a model of nonalcoholic fatty liver disease (NAFLD). SCFAs produced by *L. plantarum* help activate the Nrf2 pathway, which increases the production of antioxidant enzymes and reduces oxidative stress in the liver. This pathway is essential for alleviating age-associated hepatic damage (Gupta et al., 2024).

According to Qian et al. (2018), *L. plantarum* CQPC11 was found to increase antioxidant enzymes and lower inflammation, which helps protect the liver from harm and swelling. *L. plantarum* AR113 was found to help the liver heal better by altering the gut bacteria and substances in the blood, which are affected by SCFA levels. This probiotic strain augmented hepatocyte proliferation and facilitated liver regeneration following hepatectomy (Xie et al., 2022). In studies of NAFLD, *L. plantarum* strains like ZDY2013 and DSM20174 helped improve liver health by changing the gut bacteria and boosting the production of SCFAs, which had a positive effect on metabolism and lowered fat in the liver. The potential benefits of *L. plantarum* for liver health are shown by its ability to manage the connection between the gut and liver, boost SCFA production, and activate protective signals. These actions jointly enhance liver function and diminish aging-related hepatic damage (Olotu & Ferrell, 2024); (Chen et al., 2022). *L. plantarum* can help reduce oxidative stress by turning on the Nrf2 signaling pathway, which is important for protecting cells from damage caused by oxidation. This probiotic strain affects oxidative stress by regulating multiple metabolic pathways and increasing the production of antioxidant enzymes (Tian et al., 2023).

The activation of Nrf2 by *L. plantarum* helps the liver work better, reduces fat damage, and boosts the body's ability to fight oxidation, which protects against oxidative stress. *L. plantarum* J26 increases the levels of SCFAs in the intestines, which tells the body to start the Nrf2 pathway. This activation reduces oxidative stress in the liver and helps keep mitochondria stable, which lowers cell death in cases of liver damage caused by alcohol. *L. plantarum* NA136 stimulates the AMPK pathway, thereby promoting the nuclear translocation of Nrf2. This activation boosts antioxidant pathways, which helps defend against oxidative stress in non-alcoholic fatty liver disease (NAFLD) (Zhao et al., 2023). CFSs made from lactobacilli have been shown to boost Nrf2 activity in the nucleus and increase the amounts of antioxidant genes, like heme oxygenase 1 and superoxide dismutase, in brain cells. The evidence indicates that metabolites from *L. plantarum* can influence oxidative stress responses in the brain (Di Chiano et al., 2024). Strains of *L. plantarum*, like FC225, boost the amounts of Nrf2 and related antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, in mice that eat a high-fat diet. This increase correlates with reduced lipid peroxidation and enhanced antioxidant defenses (Gao et al., 2013). The *L. plantarum* strain CGMCC 6888, when activated by catalase, boosts the production of Nrf2 and related antioxidant enzyme genes, providing strong protection against harmful reactive oxygen species (ROS) in intestinal cells. *L. plantarum* P101 helps protect the liver from damage caused by cyclophosphamide by activating the Nrf2/ARE signaling pathway, which boosts the antioxidant defense system and reduces liver cell death. The substance made by *L. plantarum* helps keep HepG2 cells safe from damage caused by H₂O₂, and this protection lessens when Nrf2 is blocked, showing how crucial Nrf2 is for these benefits.

L. plantarum has great potential for treatment because it influences the production of SCFAs and the Nrf2 signaling pathway, both of which are key for addressing various health problems related to metabolism and oxidative stress. The probiotic can help keep gut bacteria in balance and raise SCFA

levels, while also activating the Nrf2 pathway, showing a comprehensive way to treat diseases (Chen et al., 2022). These processes have been researched in diseases like type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and liver damage caused by oxidative stress, showing their wide potential for treatment. *L. plantarum* HAC01 has been shown to help diabetic mice improve how their bodies use glucose and respond to insulin by increasing SCFA levels, which are important for managing blood sugar and insulin function (Lee et al., 2021). Giving *L. plantarum* strains like DSM20174 and NKK20 boosts the production of SCFAs, which helps lower liver fat and inflammation, stopping NAFLD from getting worse. *L. plantarum* changes the types of bacteria in the gut, increasing the number of bacteria that produce SCFAs, which are beneficial for metabolic health and may lower the chances of metabolic diseases. The substances made by *L. plantarum* can trigger the Nrf2 pathway, which helps protect liver cells from damage caused by oxidative stress. This pathway is essential for alleviating liver damage induced by alcohol and other oxidative stressors (Rezgui et al., 2023; Li et al., 2024). Researchers have linked the activation of Nrf2 signaling by *L. plantarum* to improved heart function, indicating its potential contribution to heart health management. *L. plantarum* metabolites can influence how microglial cells react through the gut-brain connection, enhancing antioxidant defenses by activating Nrf2, which might help protect the brain from diseases. *L. plantarum* has been found to make colorectal cancer cells better by using butyrate, a fatty acid that helps fight tumors, by restoring the function of SMCT1, which helps take in butyrate. Such activity indicates a possible function in surmounting chemoresistance in cancer treatment (Kim et al., 2022).

RQ3: How do SCFAs from *L. plantarum* molecularly activate Nrf2 and trigger antioxidant gene expression in host cells?

L. plantarum has a complex way of fighting free radicals, mainly by making SCFAs and activating the Nrf2 signaling pathway. SCFAs act as signals that trigger the Nrf2 pathway, which is important for lowering oxidative stress and keeping cells balanced (Table 5).

Table 5. The SCFAs from *L. plantarum* activate Nrf2 and start the expression of antioxidant genes in host cells.

Author	Country	Result	Conclusion
Wu et al. (2023)	China	<i>L. plantarum</i> ZJ316 is good at dealing with hydrogen peroxide and can effectively remove harmful free radicals, both in its whole cells and the liquid made during fermentation, suggesting it could be a helpful antioxidant probiotic.	<i>L. plantarum</i> ZJ316 shows strong antioxidant abilities because it can resist hydrogen peroxide, effectively remove free radicals, and has high levels of antioxidant enzymes in both its cells and the liquid from fermentation.
Lin et al. (2018)	China	<i>L. plantarum</i> AR501 greatly increased the activity of a protein called Nrf2 and boosted several antioxidant genes in the liver, such as glutathione reductase and	Giving <i>L. plantarum</i> AR113 and AR501 by mouth significantly raised the antioxidant levels in mice that faced oxidative stress from D-galactose,

		others, indicating it could be a beneficial option for anti-aging health foods.	resulting in less liver damage and restoring the normal activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase.
Oladejo et al. (2024)	Nigeria	The Lactobacillus treatments were found to lower the harmful substance TNF- α and increase the antioxidant regulator Nrf2, suggesting they may help reduce oxidative stress and inflammation.	Lactobacillus treatments were found to reduce the inflammatory substance TNF- α and increase the levels of the antioxidant regulator Nrf2, suggesting they might help combat oxidative stress and inflammation.
Kong et al. (2020)	New Zealand	Lactobacillus spp. can help control oxidative stress in the gastrointestinal tract by lowering the activity of enzymes that produce harmful reactive oxygen species and influencing important proteins such as Nrf-2 and NF- κ B, which are crucial for protecting cells from oxidative stress and inflammation.	Lactobacillus spp. can help control oxidative stress in the gastrointestinal tract and the rest of the body, which may help reduce diseases caused by oxidative stress, such as inflammation and other long-term health issues. Their involvement in redox processes indicates potential advantages as probiotic supplements.
Long et al. (2022)	China	<i>L. plantarum</i> ZLP001 helps the body's defense against damage by lowering harmful substances called reactive oxygen species and malondialdehyde, while also increasing energy levels in mitochondria. Additionally, it was found to change how antioxidant enzymes are produced and increase the presence of nuclear erythroid 2-related factor 2 (Nrf2) in the nucleus, showing that the Nrf2-Keap1-ARE signaling pathway plays a role in its protective effects against oxidative stress.	The findings help us understand how <i>L. plantarum</i> ZLP001 reduces oxidative stress, suggesting it could be a helpful treatment or protection for animals facing oxidative stress.

Kusumo et al. (2019)	Indonesia	Probiotic treatment with <i>L. plantarum</i> IS 10506 significantly raised acetate levels in women with functional constipation ($p=0.032$), while propionate and butyrate had only minor effects ($p=0.063$ and $p=0.068$, respectively), showing a positive impact on short-chain fatty acid levels.	Taking the probiotic <i>L. plantarum</i> (IS 10506) significantly increased the levels of SCFA, especially raising acetate levels in women with functional constipation, while it had only slight effects on propionate and butyrate levels.
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From the 6 articles reviewed, it is understood that the probiotic's capacity to bolster antioxidant defenses and mitigate oxidative damage is extensively documented in numerous research studies. *L. plantarum* raises SCFA levels in the intestines, which is important for turning on the Nrf2 signaling pathway. This activation reduces oxidative stress in the liver by keeping mitochondria stable and lowering cell death, particularly when the liver is damaged by alcohol (Li et al., 2024a). The Nrf2 pathway is also activated by substances made by *L. plantarum*, including saturated fatty acids and amino acids. These compounds increase the production of protective enzymes, which helps reduce oxidative damage in HepG2 cells. *L. plantarum* strains, like FC225, are excellent at fighting off harmful substances by boosting the body's ability to neutralize different radicals and increasing the activity of antioxidant enzymes like superoxide dismutase and glutathione peroxidase. This improvement happens by activating Nrf2, which also improves fat levels in people with high cholesterol (Gao et al., 2013). The substances produced by the probiotic help lessen signs of oxidative stress, like fat damage and inflammation, which boosts its protective function in cells through a process that relies on Nrf2.

SCFAs help trigger the Nrf2 signaling pathway through *Lactobacillus plantarum*, which leads to many health benefits. SCFAs, which are mostly made when gut bacteria digest dietary fibers, send signals that help the body handle oxidative stress through the Nrf2 pathway. This relationship is crucial in alleviating diseases associated with oxidative stress, including hepatic damage and neurodegeneration. SCFAs like acetate, propionate, and butyrate are made when gut bacteria break down food fibers. These substances act as messengers that can influence the body's functions by turning on pathways like Nrf2, which are important for protecting against damage and keeping cells stable. SCFAs can activate the Nrf2 signaling pathway, which helps produce antioxidant enzymes and protective proteins for cells. This activation mitigates oxidative stress and inflammation, therefore safeguarding tissues from harm (Li et al., 2024; Rezgui et al., 2023). When the liver is damaged by alcohol, short-chain fatty acids made by *L. plantarum* can activate the Nrf2 pathway, which helps reduce oxidative stress and improve how the liver works. Improved mitochondrial function and decreased lipid buildup mitigate liver injury (Liu et al., 2018). Short-chain fatty acids, particularly butyrate, can increase Nrf2 levels in the brain, which helps reduce oxidative stress and inflammation. This process is advantageous in safeguarding against neurodegenerative illnesses and cognitive deficits (Wang et al., 2022). SCFAs can improve heart health by enhancing antioxidant protection and helping blood vessels work better, as shown in heart function studies.

L. plantarum can greatly affect how well it works to reduce oxidative stress in different treatments. This variety can be attributed to things like genetic differences, existing health conditions, and the specific strain of *L. plantarum* used (Huang et al., 2019). The efficacy of *L. plantarum* in mitigating oxidative stress has been proven in numerous research studies; however, the extent of benefits

may differ among individuals according to these factors. *L. plantarum* has been found to boost the activity of antioxidant enzymes by using pathways like KEAP1-NRF2/ARE, which turn on genes that help protect against oxidative stress. This process is essential for mitigating oxidative stress. The probiotic affects various signaling pathways, like PI3K-AKT and NF- κ B, that help lower inflammation and oxidative stress. *L. plantarum* strains show strong abilities to neutralize free radicals, which is important for reducing oxidative damage. In triathletes, taking *L. plantarum* PS128 helped reduce signs of oxidative stress and improved their performance, showing it could be a useful supplement for athletes. Peptides from rice fermented with *L. plantarum* that have antioxidant properties have been found to help protect animals' skin from damage caused by UVA rays. *L. plantarum* has been shown to help reduce oxidative stress and improve gut health in studies related to blood flow issues and inflammatory bowel disease (IBD). The probiotic demonstrates potential in mitigating oxidative stress-related symptoms in cancer and liver illnesses; however, more clinical research is necessary to validate these effects (Zhao et al., 2023). Different types of *L. plantarum*, like ZS62 and ZJ316, work better in different situations, highlighting the need to choose the right strain for medical use (Wu et al., 2023). An individual's genetic composition and environmental circumstances, including food and pre-existing health issues, can affect the efficacy of probiotics (Sun et al., 2023).

The SCFAs, the Nrf2 signaling pathway, and *L. plantarum* working together offer interesting ways to fight against oxidative stress and free radicals. SCFAs, such as acetate, propionate, and butyrate, are produced by gut bacteria when they digest food fibers, and they, along with *L. plantarum*, help lower oxidative stress by turning on the Nrf2 pathway (Dong et al., 2022). This route is essential for cellular protection against oxidative damage, and its activation can result in the production of antioxidant enzymes that alleviate oxidative stress. SCFAs, including acetate, propionate, and butyrate, are generated through the fermentation of food fibers by gut bacteria. These substances can activate the Nrf2 signaling pathway, which is vital for preserving balance in the body's redox state and protecting against oxidative stress and mitochondrial issues (Beltrán-Velasco et al., 2024). SCFAs can inhibit inflammation and carcinogenesis, highlighting their potential as therapeutic agents in conditions such as diabetes and cancer (González-Bosch et al., 2021). The Nrf2 pathway serves as an essential cellular defense system against oxidative damage. It modulates the expression of antioxidant proteins that safeguard against oxidative damage induced by injury and inflammation (Senger et al., 2016). When Nrf2 is turned on, it starts making genes that help the body clean out toxins and protect against oxidative damage, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1). Adding cofactors like alkyl catechols boosts the activation of the Nrf2 pathway, providing extra protection against oxidative stress. Strains of *L. plantarum* can activate the Nrf2 pathway, which increases the function of antioxidant enzymes and reduces oxidative stress in various tests (Wang et al., 2021). *L. plantarum* J26 improves liver health by increasing SCFA levels, which helps activate the Nrf2 pathway to reduce liver damage caused by alcohol. Other strains, like *L. plantarum* FC225 and NA136, can reduce fat levels and boost the body's defenses against damage by changing how fat is processed and activating the Nrf2 pathway. The combination of SCFAs and *L. plantarum* can activate the Nrf2 pathway better, providing strong protection against oxidative stress. The substances made by *L. plantarum*, like small-molecule peptides, can protect cells from damage caused by oxidation by turning on the Keap1-Nrf2 signaling pathway (Tang et al., 2017). These tactics underscore the efficacy of dietary treatments and probiotics in the management of disorders associated with oxidative stress.

Conclusion

L. plantarum increases SCFA levels in the intestines, which acts as a signal to activate the Nrf2 pathway. This activation is crucial for reducing oxidative stress and maintaining mitochondrial balance.

This study aims to review several research papers that explore and highlight how *L. plantarum* makes SCFAs to activate Nrf2, specifically the strategies it uses to combat free radicals. The study found that SCFAs made by *L. plantarum* are important signals that trigger the Nrf2 signaling pathway, which helps protect cells from damage caused by oxidation and inflammation. *L. plantarum* is a beneficial probiotic that uses SCFAs to trigger the Nrf2 pathway, providing strong protection against free radicals and supporting various health benefits. This research suggests that in the future, *L. plantarum* could be used not only as a regular probiotic, but also as a special ingredient in health foods and treatments aimed at reducing oxidative stress and inflammation by activating the Nrf2 pathway. While the current research points to the importance of *L. plantarum* for health, especially concerning oxidative stress, we need more thorough and varied studies involving humans to confirm these results and make them useful in everyday health applications. Future research on *L. plantarum* should focus on detailed studies of how it works, strong clinical trials with people, and exploring the effects of different strains to fully realize its benefits as a helpful probiotic for various health uses.

Conflict of interest

No Conflict of interest

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