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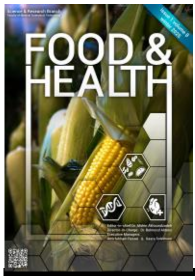

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Journal

The Anti-inflammaging Effects of Lactobacillus Plantarum by Targeting Nrf2 Signaling Pathway

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ABSTRACT

Aging is closely associated with chronic, low-grade inflammation, a phenomenon known as "inflammaging," which contributes to various age-related diseases. Emerging evidence suggests that gut microbiota, particularly probiotic strains such as Lactobacillus plantarum, can modulate inflammatory responses and oxidative stress, potentially mitigating the effects of inflammaging. Oxidative stress is widely recognized as a leading factor in inflammation and aging, resulting from an imbalance between oxidants and antioxidants, which can lead to senescence-related diseases. Nrf2 plays a pivotal role in regulating antioxidant reactions. The activation of the Nrf2 pathway represents a promising therapeutic approach for preventing senescence-related conditions.

Lactobacillus plantarum from gerobiotics could improve the antioxidant capacity of senescent cells. The focus of this systematic review is centered on exploring the association between specific strains of Lactobacillus plantarum and the Nrf2 pathway and evaluating their potential effects on disease management and anti-inflammatory interventions. By modulating redox homeostasis, L. plantarum may serve as a promising therapeutic strategy to counteract inflammaging and improve healthspan. Further research is warranted to elucidate its molecular mechanisms and potential clinical applications.

Introduction

probiotics are live bacteria and yeasts that can perform health-promoting acts for the host. Synbiotics is a term that refers to both probiotics and prebiotics. The most frequently used bacterial genera in probiotic products are Lactobacillus and Bifidobacterium (1). With more research every year, the list of probiotics benefits continues to expand, attracting considerable attention as a potential treatment option. Probiotics have been demonstrated in studies to improve healing in a variety of clinical conditions, including intestinal activity balance, immune system enhancement, infantile diarrhea, female uro-genital infections, and surgical infections. They also aid in cardiovascular health and skin conditions (2-6) and are well-known for their antioxidant properties.

Lactobacillus plantarum (also known as *Lactiplantibacillus plantarum*) is a gram-positive bacteria that belongs to the Lactic acid bacteria (LAB) diverge group, and it is shown to have significant probiotic effects (2). It can be found in a variety of vegetables, meats, fruits, dairy products, fish products, fermented foods, and beverages (3-8). (table 1)

Table 1. Isolated strains of *Lactobacillus plantarum* from fermented foods.

Food	L. plantarum strains	Reference
fruit samples (orange and lemon)	Lactobacillus plantarum (MZ707748) and Lactobacillus plantarum (MZ729681)	(9)

Table 1 (continued): Isolated strains of *Lactobacillus plantarum* from fermented foods.

Food	L. plantarum strains	Reference
fermented cabbages	Lactobacillus plantarum FC225	(10)
fermented paocai	Lactiplantibacillus plantarum DMDL 9010 (LP9010)	(11)
Kimchi	Lactobacillus plantarum—LRCC5193 (LP-LRCC5193)	(12)
fermented soybean	L. plantarum strain 4_3	(13)
fermented Yoghurt	Lactobacillus plantarum	(14)
cucumber	Lactobacillus plantarum NCDC 021	(4)
Apulian wine	Lactobacillus plantarum	(6)
Dairy food products	Lactobacillus plantarum	(7)
Rumen(cow)	Lactobacillus plantarum	(7)
yak yogurt	lactobacillus plantarum LZU-J-TSL6 and LZU-S-ZCJ	(15)
meat and meat products	Lactobacillus plantarum	(5)

This strain has been shown to be beneficial as a probiotic, as it exhibits many of the qualities required to classify a bacterium as such, including resistance to gastrointestinal conditions. It is essential for any probiotic strain to have the ability to survive in harsh digestive conditions so it can perform beneficial roles to the host. *L. plantarum* showed good tolerance to low pH conditions and could survive in the human gastrointestinal environment (11, 16). It is also well-known for its ability to adhere to extracellular matrix components and/or intestinal mucosa, which can aid in inhibiting pathogen colonization and promoting mucosal repair. They almost certainly play a role in antimicrobial activity. (17) The most common cues are rivalry for aliment and adhesion space, promotion of pathogen-harming environmental conversion, and synthesis of antibacterial compounds such as bacteriocin (17). According to research, *L. plantarum* exhibits significant antioxidant activity and shows promising potential in this regard.

A variance between increased levels of reactive oxygen species (ROS) and the low activity of antioxidant systems is designated as oxidative stress. Oxidative stress can have some beneficial effects, including the adaptation of our physiology and regulation of intracellular signal transduction. However, it is also widely known to be harmful. This is due to the fact that biological molecules can be attacked by oxygen-free radicals, which can result in the onset of diseases associated with a particular lifestyle, including cancer, diabetes mellitus, atherosclerosis, and hypertension. Lifestyle habits such as drinking alcohol, smoking, a high-fat diet, and fatigue can result in oxidative stress in humans due to the presence of excessive ROS in the body (18).

L. plantarum can boost the expression of the Nrf2/keap1 pathway, resulting in antioxidant activity. The focus of this systematic review is centered on exploring the association between specific strains of *lactobacillus plantarum* and Nrf2 pathway and evaluating their potential effects on oxidative stress and anti-inflammaging interventions.

1) Antioxidant effect and Nuclear factor erythroid 2-related factor 2 (Nrf2)

This gene encodes a transcription factor that plays a crucial role in regulating genes containing antioxidant response elements (AREs) within their promoters. A significant portion of these genes encode proteins associated with injury and inflammation responses, including the modulation of free radical production (19) and regulation of cytoprotective responses that reduce damage caused by various environmental stressors.

The activation of the Keap1/Nrf2/ARE signaling pathway is known to stimulate the expression of antioxidants at high levels. These antioxidants include γ-glutamylcysteine synthetase (γ-GCS), NAD(P)H : quinone oxidoreductase 1 (NQO1), and heme oxygenase 1 (HO-1) (20). This signaling pathway has been shown to have a protective effect on animal models and is crucial as a mechanism for antioxidant defense. (Figure 1)

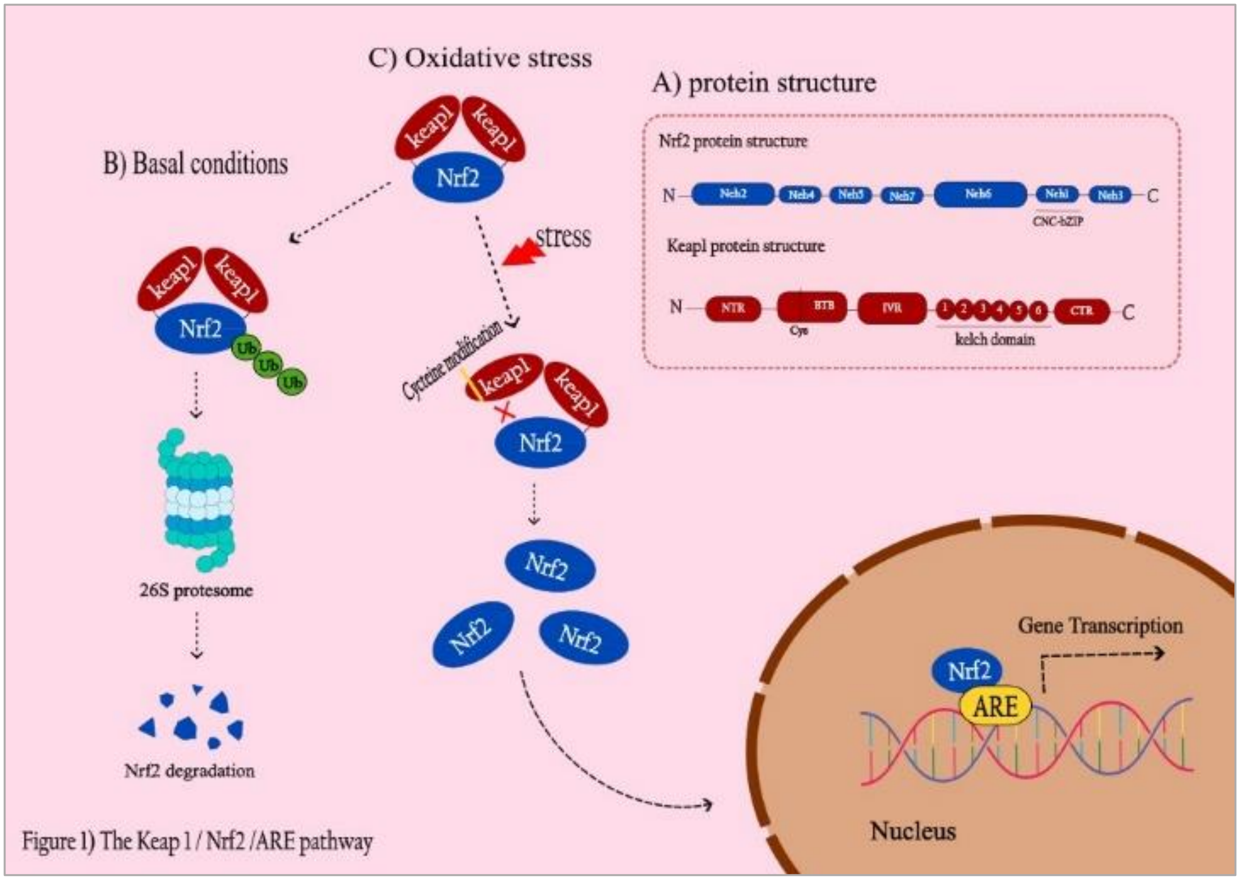

Figure 1) The Nrf2 protein is composed of seven different domains, each with its own distinct purpose. A conserved basic region-leucine zipper (bZIP) architecture is an important attribute of the Neh1 domain. Under usual circumstances, the BTB domain situated within the Keap1 protein facilitates interaction with the Cul3 protein, thereby promoting its ubiquitination. As a result, the Nrf2 undergoes degradation through the proteasome pathway. Upon exposure to oxidative stress, Keap1 engages in an alteration, resulting in a structural conversion of the Keap1-Cul3-E3 complex. This inhibits the ubiquitination process of Nrf2, allowing Nrf2 to form a complex with sMaf proteins and bind to the ARE (antioxidant response element) region.

Notably, some *Lactobacillus* species found in traditionally fermented foods and drinks provide a long-term supply of alkyl catechols, which act as natural Nrf2 inducers (21).

Multiple strains *of Lactobacillus plantarum* have been recognized for their antioxidant properties, primarily attributed to their ability to modulate the Nrf2 pathway. In a study by D. Gao and colleagues, the antioxidant and hypolipidemic effects of wild *Lactobacillus plantarum* FC225 in high-fat diet-fed mice were studied. The findings suggest that FC225 hypolipidemic and antioxidant protective effects through the mediation of the Nrf2 signal pathway and subsequent expression of antioxidant enzymes (10).

In a study by Guangqing Mu et al., *Lactobacillus plantarum* Y44 was shown to effectively gather oxygen-free radicals and preserve the integrity of Caco-2 cells by upregulating the expression of β-catenin and E-cadherin in ABAP-damaged Caco-2 cells. Furthermore, the study revealed that *L. plantarum* Y44 activates the Nrf2 signaling pathway. These observed antioxidant effects are attributed to the ability of *L. plantarum* Y44 to neutralize oxygen-free radicals and stimulate the Nrf2/Keap1 signaling pathway to activate (22).

Research studies have shown that Lactobacillus plantarum CQPC11 can enhance the expression of Nrf2 and reduce the expression of iNOS in the liver and spleen of mice. Based on the findings, it appears that L. plantarum CQPC11 holds promise in potentially mitigating the effects of oxidation and aging in mice (23).

L. plantarum K41, which has shown significant antioxidant activity and has been studied for its potential use in various health applications, such as reducing the severity and incidence of tooth decay. (24) other strain such as KSFY06 (25), AR501 (26), C88, NJAU-01 (27) take part in antioxidant activity as well.

While these strains have been studied explicitly for their antioxidant roles, it is worth noting that other strains of *Lactobacillus plantarum* may also possess antioxidant properties. The degree of antioxidant activity may vary among different strains due to variations in their genetic makeup and physiological characteristics.

2) Effect of different *Lactobacillus plantarum* strains

Different strains of *Lactiplantibacillus plantarum can exhibit various anti-aging properties, which can be utilized as clinical options, nutritional supplements,* and more. Our study aims to investigate the impact of *lactobacillus plantarum* and provide valuable insights into this area.

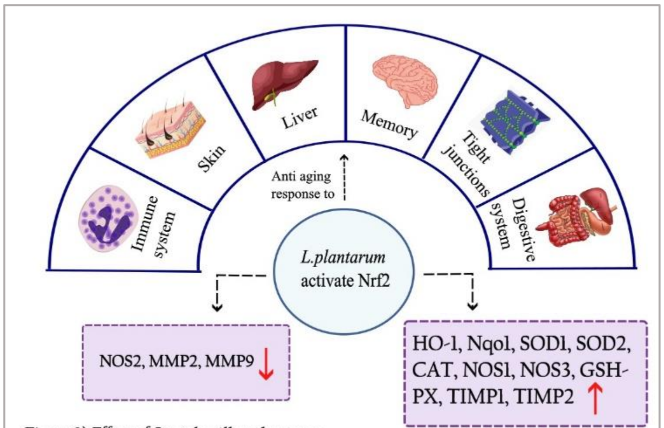

Figure 2) Effect of *Lactobacillus plantarum*

2.1) Delaying aging processes in cells

Aging is a complex process that involves several factors, including lifestyle habits, epigenetics, and genetics. Modifying these factors can sometimes help delay or reverse the aging process (28).

Through various mechanisms, Nrf2 activation can prevent cell aging. It not only has the ability to increase antioxidant response but can also have positive effects on tissues by reducing the expression of specific genes, such as NOS2 in the liver, or MMP3 and MMP9 in the skin (29). NOS2 is known to produce reactive free radicals in the liver by synthesizing nitric oxide (30). At the same time, MMPs are typically involved in the breakdown of the extracellular matrix (31), which can shorten the lifespan of the cell.

Lactobacillus plantarum successfully activates the Nrf2 pathway, thereby enhancing antioxidant activity and preventing reactive oxygen species, oxidation, and inflammation in cells.

Many *L. plantarum* strains can be used to reduce inflammation, resulting in anti-aging properties and inhibiting the progression of age-related conditions. *L. plantarum* strain HFY09 has been shown to have anti-aging effects on the skin and liver of mice (29).

It has been discovered that *L. plantarum* can successfully promote the proliferation of epithelial cells through the exact mechanism (32). Furthermore, L. plantarum HFY09 can restore gastric tissue injury by increasing the mRNA expression of Nrf2 and enhancing the mucosa barrier (33). In pig epithelial cells, when exposed to H_2O_2, *Lactobacillus plantarum* ZLP001 can reduce oxidative damage. J. Wang et al. propose that it has the potential to be used as a preventative or remedial treatment for animals facing oxidative stress (34).

Interestingly, *L. plantarum* LB244R reduced Crow's feet wrinkles and increased skin hydration and elasticity, showing an impressive anti-aging outcome (35).

L. plantarum can reduce UVA-induced photoaging by shielding fibroblast cells and boosting their levels of collagen and elastin (36). In a double-blind clinical trial, researchers observed that *Lactobacillus plantarum* HY7714 improved skin hydration, decreased wrinkles formation, improved skin elasticity by decreasing inflammation, and improved tight junction status (37). It can also prevent photoaging by blocking UVB-induced effects (38).

Another possible treatment for alcohol-induced gastric injury is *L. plantarum* ZS62. The results of the experiment showed that it can raise the tissue's levels of antioxidant and anti-inflammatory chemicals by activating the Nrf2 pathway (39). *L. plantarum ZS62 also demonstrated encouraging results for reducing* LPS-induced acute liver injury by Decreasing the activity of genes linked to inflammation and increasing the activity of genes involved in lipid and oxidative metabolism. It might be applied as a therapeutic option for individuals who consume large amounts of alcohol (40).

Around the world, alcoholic liver disease (ALD) continues to be a leading cause of morbidity and mortality which there is currently no effective treatment. Unhealthy daily habits such as heavy drinking and smoking can also increase the chances of liver damage. Research suggests that probiotics, particularly *lactobacillus*, can be widely used as a treatment option for liver injury. The liver's crucial role in detoxifying LPS can be aided by upregulating Nrf2, which reduces liver injury by elevating antioxidant activity (41).

Lactobacillus plantarum KLDS 1.0386 effectively reduced LPS-induced acute liver injury by positively regulating gut microbiota, increasing SCFA levels, and inhibiting alcohol-induced lipid aggregation and oxidative stress in liver (42, 43). *L. plantarum* NA136 has also been proven to have a beneficial effect on liver injury (44).

It has been shown that *Lactobacillus plantarum* LZU-J-TSL6 has similar effects in reducing the impact of liver aging (15). *L. plantarum* KSFY06 can help preserve health by preventing acute liver injury induced by D-galactose/LPS. (25) By decreasing GPR78 and CHOP protein expression and encouraging the restoration of endoplasmic reticulum (ER) homeostasis, L. plantarun AR113 can activate cell anti-apoptotic pathways and reduce liver injury (45). A 4-week treatment with *Lactobacillus plantarum* Lp2 resulted in a significant improvement in oxidative injury and apoptosis, demonstrating its usefulness in preventing liver injury (46, 47).

In a study conducted on zebrafish, *treatment with Lactobacillus plantarum significantly decreased liver damage and protected the organism by triggering the Keap/Nrf2 signaling pathway* (48).

2.2) Boost immune system

Numerous studies have been conducted to substantiate the immune system-enhancing effects of Lactobacillus plantarum (9). During a study led by J. Wang et al., it was observed that Lactiplantibacillus plantarum JLAU103 not only protects cells against oxidative stress by activating antioxidant enzymes and the Nrf2 pathway but also enhances intestinal mucosal barrier function and promotes the production of short-chain fatty acids through the activation of the MAPK pathway. These mechanisms have been shown to initiate the activation of mice's systemic immunity (49). Therefore, Probiotics can be useful for infection control, particularly in elderly individuals who face a higher mortality rate and organ dysfunction. It is safe to assume that probiotics can play a significant role in maintaining their health (50). Probiotics were deemed by the World Health Organization in 1994 to be the next most important component of the immune system, after antibiotics, in terms of combating antibiotic resistance (51).

2.3) Increase metabolism and promote weight loss

It has been discovered that probiotics can have a noteworthy impact on metabolism.By supplementing Lactobacillus plantarum TWK10, there was an increase in the number of type I fibers in the muscle, also known as slow muscle, as well as an improvement in endurance during exercise (52). Following *the ingestion of Lactobacillus plantarum LLY-606*, the proline metabolism pathway was enhanced (53). *Lactobacillus plantarum* KSFY01 can enhance exercise tolerance and induce antioxidant effects in mice, potentially improving athletic performance (54). *L. plantarum* NA136 has also been shown to reduce body weight gain and adipose tissue mass (44). In a study conducted on hyperlipidemic mice, it was demonstrated that *L. plantarum* CAI6 and SC4 can help regulate lipid metabolism and prevent cardiovascular disease (55).

2.4) Avert neurodegeneration and memory loss

Lactobacillus plantarum has been shown to enhance the expression of neurodegenerative and neurotrophic factors within the hippocampus (56). *L. plantarum produces remarkable outcomes in subjects with neurological diseases*. Mice were tested with *L. plantarum X7022 to see if it could improve memory properties, which led to enhanc*ed learning. It additionally stabilized neurons by controlling apoptosis, AChE overexpression, and amyloid-β deposition. Additionally, it affected neuronal functions by controlling CREB-BDNF signaling pathways and iNOS expression (57).

According to a study by Wan Wang et al., it is suggested that Lactobacillus plantarum 69-2, combined with galactooligosaccharides (GOS), can prevent neurodegeneration and improve memory. The authors infer that

the present study could pave the way for the creation of aging-related supplements, with the involvement of gut microbiota (58). Interestingly, *Lactobacillus plantarum* DP189 can delay neurodegeneration by Regulating oxidative damage, thereby suppressing Parkinson's disease (59). In another study conducted on diabetic rats, it was found that *L. Plantarum* can enhance learning by improving gut microbiota composition and reducing oxidative stress (60). The following table (Table 2) presents some of the known strains and properties for reference.

Table 2. *Lactobacillus plantarum* strain and its antioxidant effects.

L. plantarum strain	Main effects	Reference
MZ707748 and MZ729681	Enhance immune system Block a variety of signaling pathways associated with inflammation activity	(9)
KLDS 1.0386	Prevent liver injury with reduce LPS levels, elevate SCFA and inhabit alcohol-induced liver lipid	(42, 43)
FC225	Antioxidant protection Increase expression of antioxidant enzymes	(10)
KSFY06	Antioxidant and anti-inflammatory properties Prevents D-gal/LPS-induced ALI	(25)
AR501	The increase in antioxidant status	(26)

Table 2 (continued): Lactobacillus plantarum strain and its antioxidant effects.

L. plantarum strain	Main effects	Reference
Y44	Anti-inflammatory and antioxidant properties Activation of Nrf2 signaling pathway	(22)
JLAU103 (EPS103)	Protects against oxidative by enhancement of tight-junction proteins improve the physical barrier functions of the intestine	(49)
ZLP001	Protect cells from oxidative damage induced by H2O2 resulted in a Reduction of H2O2-induced oxidative damage	(34)
HFY09	Minimize signs of aging and slow down the aging process	(29)
LB244R®	Reduced wrinkles and raised skin hydration and elasticity	(35)
HY7714	Reduced wrinkles and raised skin hydration and elasticity	(37)
ZS62	Protect gastric mucosa from gastric injury Prevent liver injury by Decreasing the activity of genes linked to inflammation	(39)
CAI6	Regulates lipid metabolism Prevent cardiovascular disease	(55)
Lp2	Reduce liver injury by treating oxidative injury and apoptosis	(46, 47)
NA136	Prevent liver injury Reduce body weight gain and adipose tissue mass	(44)
LLY-606	Increase metabolism pathway	(53)
KSFY01	Improve exercise tolerance	(54)
X7022	Stabilize neurons by controlling apoptosis and improve memory properties	(57)
DP189	Delay neurodegeneration	(59)
AR113	Can decrease ER stress and cell apoptotic pathways preventing liver injury	(45)
TWK10	Increase muscle mass and improves exercise performance	(52)

3) Conclusion

Numerous *Lactobacillus* strains possess antioxidant qualities; however, it has been noted that the level of antioxidant activity varies amongst *Lactobacillus* strains. In this paper, we specifically collect insight on the antioxidant and anti-aging capabilities of *Lactobacillus plantarum*.

It has been determined that certain strains of Lactobacillus plantarum, including K41, C88, 299v, P8, and WS51, possess antioxidant properties. These strains produce enzymes and antioxidant compounds that help reduce oxidative stress and neutralize free radicals. The *L. plantarum* strains KSFY06, ZS62, LZU-J-TSL6, NA136, and KLDS1.0344 demonstrated promise in reducing acute liver injury caused by LPS. Furthermore, Y44, ZLP001, and HY7714 showed promise in lessening signs of aging and possibly delaying the aging process. Moreover, *Lactobacillus plantarum* JLAU103 has a reputation for enhancing immunity. also *lactobacillus plantarum* DP189 enhances memory and *L.plantarum* KSFY01,NA136, CAI6 and SC4 aids in weight loss.

Overall, information gathered by articles highlights the potential applications of different *L. plantarum* strains in antioxidative therapy, liver injury mitigation, and anti-aging interventions through activation of the Keap1/Nrf2/ARE signaling pathway, which reduces inflammation and reactive oxygen species.

However, further clinical and preclinical investigations are necessary to evaluate the efficacy of probiotic treatment comprehensively.

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