

New lactic acid bacteria for skin health via oral intake of heat-killed or live cells

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Abstract

Lactic acid bacteria play an essential role in the food industry in the manufacture of many fermented products (cheese, yogurt, fermented vegetables, etc.). Application of these organisms is now being extended to the area of health improvement, as their probiotic activities become known. Probiotics are defined as viable microorganisms that exert a beneficial effect on the health of the host when they are ingested in sufficient quantity. Lactic acid bacteria and bifidobacteria isolated from the human intestine are the most common probiotics used for human consumption. The development of new probiotics with new beneficial effects is eagerly awaited in the food industry. This review introduces *Lactococcus*, which are one of the genera of lactic acid bacteria and are mainly isolated from dairy products and fermented vegetables, as new probiotics, focusing especially on *Lactococcus lactis* H61, which improves skin status in Japanese women with oral intake of heat-killed or live cells. The deduced mechanisms associated with the beneficial effects of strain H61 are also discussed.

KEYWORDS

Lactococcus, probiotics, skin health

1 | INTRODUCTION

Lactic acid bacteria consist of 26 genera now, and play an essential role in the food industry in the manufacture of many fermented products (cheese, yogurt, fermented vegetables, etc.). Application of these organisms is now being extended to the area of health improvement, as their probiotic activities become known. Probiotics have been defined as viable microorganisms that exhibit a beneficial effect on the health of the host when they are ingested in sufficient quantity (Lee & Salminen, 1995). Probiotics have been shown to reduce serum cholesterol levels (De Rodas, Gilliland, & Maxwell, 1996), improve the balance of intestinal microflora (Lidbeck et al., 1991), and exert immunomodulatory activity (Kalliomaki, Salminen, Pousa, Arvilommi, & Isolauri, 2003). Lactobacilli and bifidobacteria isolated from the human intestine are the most common probiotics used for human consumption. In contrast, there are few studies on the probiotic activities of the genus *Lactococcus* since they are not

considered to be natural inhabitants of the human gastrointestinal tract (Teuber, Geis, & Neve, 1992). However, several studies have shown that certain strains of *Lactococcus* can survive to reach the human and animal gastrointestinal tracts (Grahn, Holm, Lilja, & Sellgren, 1994; Kimoto, Nomura, Kobayashi, Mizumachi, & Okamoto, 2003). Since lactococci are widely used as starter bacteria in the manufacture of cheese and other fermented dairy products, establishing the effective probiotic properties of lactococci could lead to the development of new probiotic foods. My coworkers and I previously reported that *Lactococcus lactis* isolated from dairy products and plants had probiotic activities that improved lipid metabolism (Lee et al., 2005) and showed immunomodulatory activity (Kimoto, Mizumachi, Okamoto, & Kurisaki, 2004; Yoshida et al., 2011). In addition, Maruo et al. (2012) reported that oral administration of fermented milk made by *Lactococcus lactis* subsp. *cremoris* FC protects mice against influenza virus infection. Sugimura et al. (2015) reported that intake of *Lactococcus lactis* subsp. *lactis* JCM5805

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prevents the pathogenesis of an influenza-like illness in humans. Furthermore, it is reported that *Lactococcus* sp. strain 20-92 isolated from healthy human feces produces equol, thought to have potent estrogenic activity, from daidzein (Shimada et al., 2012). Lactic acid bacteria including *Lactococcus lactis* likely have additional probiotic activities.

As the elderly population increases, the prevalence of aging-related diseases will increase, and functional foods that provide health benefits to control aging and prolong a healthy lifespan will become more desirable. Various compounds have been reported to contain functional molecules that have anti-aging effects. As for lactic acid bacteria and bifidobacteria, it is reported that *Lactobacillus casei* strain Shirota activates immune responses in aged mice and ameliorates influenza viral infections (Hori, Kiyoshima, Shida, & Yasui, 2002), and that oral administration of *Lactobacillus gasseri* TMC0356 increases splenic natural killer (NK) cell activities in senescence-accelerated mice (Kawase et al., 2012). Lee et al. (2016) reported that *Lactobacillus reuteri* BM36301 was a potential probiotic strain because it showed anti-inflammatory activity in aged mice. The probiotic *Lactobacillus johnsonii* La1 (NCC533) decreased the incidence of infection in elderly people (Fukushima et al., 2007).

In this review, I will first introduce the beneficial effects that *Lactococcus lactis* subsp. *cremoris* H61 exerts on the suppression of aging deterioration: it has been reported that oral administration of heat-killed cells of this strain to aged senescence-accelerated mice was associated with decreased incidence of skin ulcers, reduced bone density loss, and reduced hair loss compared with those of controls that did not receive strain H61 (Kimoto-Nira et al., 2007). In addition, Oike et al. (2016) investigated the effect of administration of heat-killed strain H61 on age-related hearing loss, a common disorder associated with aging, in C57BL/6J mice, and reported that mice fed a diet containing strain H61 maintained a significantly lower auditory brainstem response threshold than control mice (i.e., those not fed strain H61), and age-related loss of neurons and hair cells in the cochlea was suppressed by the administration of strain H61.

In addition to those studies on the anti-aging effects of strain H61, investigations of strain H61 in humans have been carried out to fully explore its effect on skin health and appearance. Safety is of prime importance in the selection of new probiotic organisms (Salminen et al., 1998), and strain H61 has already been shown to be empirically safe by its use in manufacturing dairy products in Japan. Nonviable microorganisms have also been included within the definition of probiotics (Salminen, Ouwehand, Benno, & Lee, 1999). Thus, in this review, I describe the effects of heat-killed and viable strain H61 on human skin health.

2 | HUMAN TRIALS FOR SKIN HEALTH

For women, it may be said that their quality of life is affected by their skin health. Various endogenous and environmental factors, including aging, exposure to sunlight and chemicals, and mechanical damage (McCallion & Li Wan Po, 1993; Pathak, 1982), are known to

affect skin status. In addition, the consumption of various foods is thought to alter skin status (Izumi et al., 2007; Nagata et al., 2010). With regard to lactic acid bacteria and bifidobacteria, there are many studies on their effects in humans with skin trouble. Matsumoto et al. (2014) reported that oral intake of *Bifidobacterium animalis* subsp. *lactis* LKM512 may exert antipruritic effects in subjects with adult-type atopic dermatitis. It is also reported that oral intake of *Lactobacillus rhamnosus* SP1 improves the appearance of adult acne (Fabbrocini et al., 2016). In contrast, there are few reports on the effects of lactic acid bacteria and bifidobacteria on skin status in humans who are free of skin diseases.

When presented as heat-killed or as live cells, strain H61 improved the condition of the skin of senescence-accelerated mice (Kimoto-Nira et al., 2007). My coworkers and I then investigated the effects of oral supplementation with heat-killed cells of this strain on the properties of healthy human skin. In those studies, we used heat-killed cells because they are easier to handle than live cells. A double-blind, placebo-controlled trial was carried out to evaluate the effect of heat-killed cells of strain H61 on the properties of skin in Japanese women (Kimoto-Nira, Aoki, Sasaki, Suzuki, & Mizumachi, 2012a). Volunteers ($n = 30$) were randomly assigned to receive test food with or without 60 mg (approx. 4×10^{10} colony-forming units [cfu]) of heat-killed strain H61 daily for 8 weeks from October to December. Before and at the end of the treatment, skin hydration (inner forearms and cheek) and melanin content, elasticity, and sebum content (cheek only) were determined by mechanical analysis. We analyzed the effect of age on the results by dividing the subjects into three age categories (30–39 years old [30s], 40–49 years old [40s], and 50–69 years old [50s–60s]). The intervention affected only the skin hydration of the inner forearm. Compared with skin hydration at Week 0, skin hydration of the inner forearm at Weeks 4 and 8 decreased in all volunteers (except those in their 50s and 60s) because of the change from autumn to winter (Figure 1). The inner-forearm skin hydration in the oldest H61 group was maintained throughout the study. The volunteers also completed self-evaluation questionnaires (regarding skin and general health conditions) at Weeks 4 and 8. Apparent hair follicles and dryness of the throat at Week 8 improved in the H61 group overall compared with the placebo group. The H61 group in their 30s noted marked improvements in self-assessed skin elasticity at Week 8 compared with at Week 0 and compared with the placebo group at Week 8. This was the first report to demonstrate the beneficial effect of heat-killed lactic acid bacteria on skin properties and age distribution in humans free of skin diseases.

It is reported that oral intake of yoghurt made by using *Lactobacillus delbrueckii* subsp. *bulgaricus* 2038 plus *Streptococcus thermophilus* 1131 for 4 weeks improved skin elasticity and the degree of dryness in cheeks of women (Isawa et al., 2008). Mori et al. (2016) also reported that the intake of fermented milk containing *Bifidobacterium breve* strain Yakult plus galactooligosaccharides for 4 weeks increased hydration levels of the stratum corneum in women. Thus, establishing the beneficial properties of fermented milk made by using strain H61 could lead to recognition of strain H61 as an effective probiotic dairy starter. My coworkers and I conducted a randomized double-blind trial to evaluate the effects

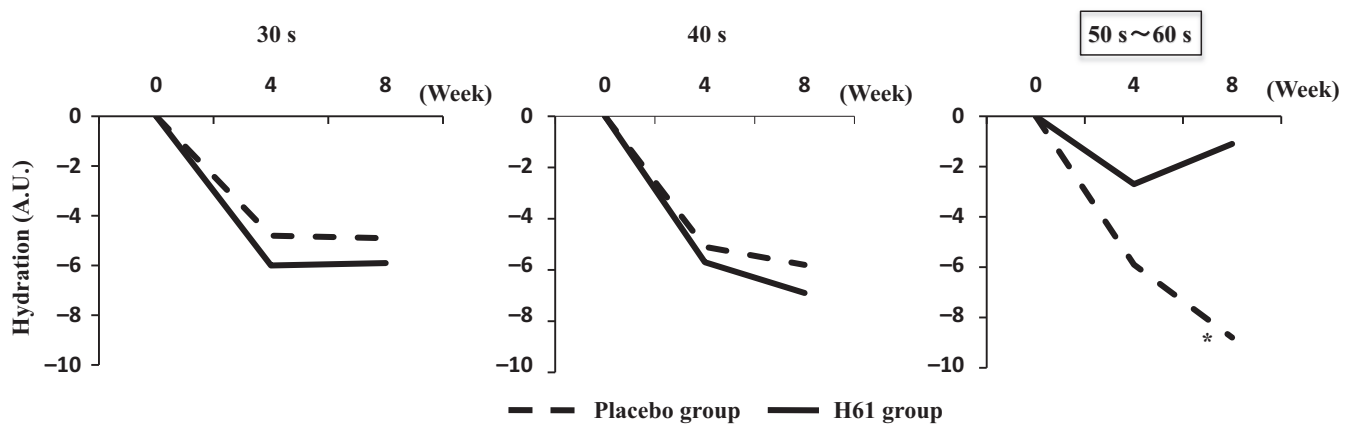


FIGURE 1 Skin hydration of the inner forearm of women in three age categories (30s, 40s, and 50s–60s) who received H61 cells or did not (placebo). A.U., arbitrary units. * $p < .05$ versus Week 0

of fermented milk produced by using only strain H61 as the starter bacterium (H61-fermented milk) on the skin properties of Japanese women (Kimoto-Nira et al., 2014b). In that study, the effects of strain H61 were compared with the effects of other lactic acid bacteria by using conventional yoghurt fermented by *L. delbrueckii* subsp. *bulgaricus* plus *S. thermophilus* as the yoghurt starter.

Healthy volunteers aged 19–21 ($n = 23$) received H61-fermented milk (10^{10} cfu of strain H61/day) or conventional yoghurt (10^{10} cfu of both *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus*/day), as a reference food, daily for 4 weeks during February to March. Before and at the end of the 4 weeks, skin hydration (inner forearms and cheek) and melanin content, elasticity, and sebum content (cheek only) were measured. Skin hydration of the inner forearm was higher at Week 4 than at Week 0 in both groups. This is likely in response to environmental changes, such as temperature and humidity, due to the transition from winter to spring. However, sebum content in the cheek rose significantly after intervention in the group receiving H61-fermented milk but not the conventional yoghurt group (Figure 2). This finding indicates that this positive effect due to strain H61 was not season-dependent. As skin lipids contribute to maintaining the skin barrier, H61-fermented milk would have beneficial effects on the skin of young women. Other skin parameters did not differ in either group.

3 | DEDUCED MECHANISMS OF THE EFFECTS

In this review, I have shown that there were beneficial effects on human skin status, independent of whether the *L. lactis* H61 cells were live or not. It is reported that intestinal microbial balance (Isawa et al., 2008), immune response (Nishimura, Tohyama, Satoh, Nishimura, & Reeve, 1999), and oxidative status (Sasaki, Kajiya, Ozeki, Okabe, & Ikebe, 2014) are all closely associated with skin properties. What is the possible mechanism whereby intake of strain H61 affects human skin status? Baba et al. (2010) reported that feeding of *Lactobacillus helveticus* CM4-fermented milk whey

decreased transepidermal water loss in mice. Are milk metabolites produced by strain H61 associated with those effects? It was previously reported that administration of strain H61 to mice, either as living cells suspended in milk or as a fermented milk made by the strain, reduced skin deterioration with aging (i.e., incidence of hair loss and skin ulcers) compared with mice administered milk, and there was no significant difference in skin status between the suspension of live cells and fermented milk (Kimoto-Nira et al., 2007). Considering that those results in mice can be extrapolated to those in humans, and that heat-killed cells provide beneficial effects on skin status in humans (Kimoto-Nira et al., 2012a), strain H61 itself, not a milk metabolite, would be associated with the improvement of skin status. The beneficial properties of live cells or heat-killed cells of strain H61 are summarized in Table 1. Below I will discuss the possible mechanisms of action.

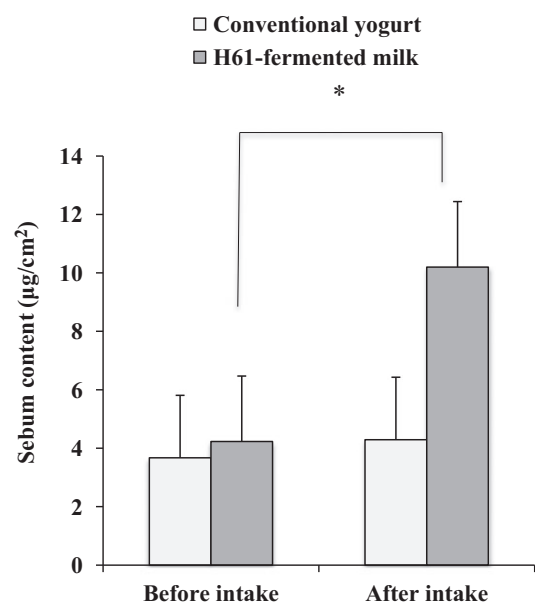


FIGURE 2 Sebum content in cheeks of women administered H61-fermented milk or conventional yogurt for 4 weeks. * $p < .05$

TABLE 1 Beneficial properties of *Lactococcus lactis* H61 in relation to skin health

	Live cells	Heat-killed cells
Improvement of intestinal microbial balance in mice ^{a,b}	–	+
Immunostimulation		
In vitro ^{c,d}	+	+
In mice ^a	ND	+
Antioxidative activity (superoxide dismutase) in vitro ^e	+	ND
Suppression of inflammation (production of leukotriene B ₄) in vitro ^f	+	ND

+, positive; –, negative; ND, not determined.

^aKimoto-Nira et al. (2007).

^bOike et al. (2016).

^cKimoto et al. (2004).

^dKimoto-Nira et al. (2012b).

^eKimoto-Nira et al. (2014a).

^fKimoto-Nira et al. (2009).

3.1 | Heat-killed cells

3.1.1 | Intestinal microbial balance

It is well known that supplementation with certain live lactic acid bacteria and bifidobacteria has beneficial effects on intestinal microbial balance. There are also studies on the effects of heat-killed cells on intestinal microbiota. For example, it is reported that oral intake of heat-killed *Lactobacillus kunkeei* YB38 affects the intestinal environment (decreasing levels of the *Bacteroides fragilis* group and fecal pH, and increasing fecal acetic acid level and bowel movements) in humans (Asama et al., 2016). My coworkers and I previously reported that administration of heat-killed strain H61 was not associated with any significant changes in viable counts of *Bacteroides*, *Bifidobacterium*, or *Enterococcus* and that the numbers of viable cells of *Lactobacillus* and *Staphylococcus* were significantly lower in feces of mice fed strain H61 than in the control mice (i.e., mice not fed strain H61) (Kimoto-Nira et al., 2007). On the other hand, we also reported that fecal analysis of bacterial flora on the basis of 16S ribosomal RNA gene sequences revealed that the administration of heat-killed cells of strain H61 increased the prevalence of *Lactobacillaceae*, which is positively correlated with hearing ability in mice (Oike et al., 2016). The difference in these results is likely to be derived from the differences between the methods used for analyzing intestinal microflora. In any case, according to the responses recorded on the self-evaluation questionnaire in the human study (Kimoto-Nira et al., 2012a), oral intake of heat-killed strain H61 had no effect on constipation or diarrhea, which are also reportedly associated with skin health (Isawa et al., 2008). These results show that the beneficial effects, including maintaining skin hydration, by oral intake of heat-killed strain H61 would not be mediated by any changes in the intestinal microflora.

3.1.2 | Immune stimulation

The components of lactic acid bacteria that stimulate vertebrate host immunity have been studied. Kitazawa, Yamaguchi, and Itoh (1992) reported that slime products produced by *Lactococcus lactis* subsp. *cremoris* KVS20 are potent B-cell-dependent mitogens. Makino et al. (2006) reported that the extracellular polysaccharides produced by *Lactobacillus delbrueckii* subsp. *bulgaricus* OLL1073R-1 had immunomodulatory effects (enhancement of NK cell activity). Sasaki, Suzuki, Fukui, and Yajima (2015) reported that cell-bound exopolysaccharides produced by *Lactobacillus brevis* KB290 enhanced cytotoxic activity of mouse splenocytes. It has been reported that the cell walls of some lactic acid bacteria can induce the production of cytokines such as interleukin-6 (IL-6) and IL-12 by macrophages (Kimoto-Nira, Suzuki, Kobayashi, & Mizumachi, 2008; Tejada-Simon & Pestka, 1999). Furthermore, the CpG motif in bacterial DNA enhances immune system responses (Krieg et al., 1995). The AT motif from lactic acid bacteria is also reported to enhance immune responses (Shimosato et al., 2005).

Oral administration of heat-killed cells of strain H61 may have anti-aging effects by influencing immune responses: analysis of spleen cells showed that mice orally administered heat-killed strain H61 produced more interferon- γ and IL-12 than did control mice (i.e., mice not fed strain H61) (Kimoto-Nira et al., 2007). My coworkers and I investigated the ability of strain H61 to induce a cellular immune response by comparing it with strain No. 13, a variant that induces lower IL-12 production than does strain H61 in experiments using macrophage-like cell lines (Kimoto-Nira, Suzuki, Aoki, Kobayashi, & Mizumachi, 2012b). Comparing a bacterial strain that has high immunostimulatory activity with a strain that has low or no activity can help to identify the factors that affect this activity and to clarify the mechanism.

Strain H61 does not produce slime products in milk and constituted medium. We focused our investigation on the cell wall components of strains H61 and No. 13. The cell wall fraction of lactic acid bacteria generally includes peptidoglycans (PGs), polysaccharides, teichoic acid, lipoteichoic acid (LTA), and cell wall-associated proteins. The contents of the sugars in the cell walls prepared from strain H61 were significantly higher than those of cell walls prepared from strain No. 13, but sugar composition in each was similar. Bacterial LTA is thought to be responsible for enhancing the immune system via Toll-like receptor 2, which is present on immunocompetent cells (Takeda, Kaisho, & Akira, 2003). Although we did not determine the teichoic acid and LTA contents, we hypothesized the sugar fraction on the cell surface, as well as the teichoic acid and LTA, may mediate the positive effect of strain H61 on IL-12 inductive activity. Qualitative and quantitative analyses of the amino acid compositions of purified PGs found no significant difference between strains H61 and No. 13 in terms of the amino acid ratio. The levels of IL-12 production induced by heat-killed cells of strains H61 and No. 13 were found to be similar, which suggests that compounds that are sensitive to heat, such as proteins, could be associated with the difference observed between these strains in the ability to induce IL-12

production. Careful purification of cellular components, including the cell wall and cytoplasmic fractions, from both strain H61 and strain No. 13 is required to identify the specific molecules that induce IL-12 production by macrophages, although this activity alone would not be responsible for the beneficial effects of strain H61 on skin health.

In contrast to those studies, it has also been reported that there is no relationship between the chemical composition of the cell wall and immune modulation in lactobacilli (De Ambrosini, Gonzalez, Perdigon, de Ruiz Holgado, & Oliver, 1996). Recently, the complete genome sequence of *Lactobacillus curvatus* FBA2—the heat-killed cells of which are reported to improve skin status in mice when orally administered—was reported (Nakano et al., 2016). Genome sequences of strains H61 and No. 13, which are now under investigation, are expected to help to clarify the mechanisms involved.

3.1.3 | Antioxidative activity

In an earlier study, my coworkers and I found that mice fed heat-killed cells of strain H61 had serum concentrations of thiobarbituric acid-reactive substances (TBARS) similar to those in control mice (i.e., mice not fed strain H61), indicating that lipid peroxidation status was not associated with the anti-aging phenomenon (Kimoto-Nira et al., 2007). However, the TBARS index only partly represents oxidative damage. We are currently investigating potential additional antioxidative effects of heat-killed strain H61, including suppression of oxidative damage of DNA and suppression of reactive oxygen species generation. In our preliminary study, heat-killed cells of strain H61 showed an antioxidant effect by scavenging the α,α -diphenyl- β -picrylhydrazyl radical. The relationship between the beneficial effects of oral administration of heat-killed cells of strain H61 and the peroxidation status in vivo will be the subject of a further study.

3.2 | Live cells

3.2.1 | Intestinal microbial balance

It has been suggested that bacteria ingested as probiotics cannot affect the intestinal environment unless their population reaches a certain minimum level of between 10^6 and 10^8 cfu/g of intestinal content (Marteau & Rambaud, 1993). In order to accumulate in the intestinal tract, ingested bacteria must be resistant to the enzymes in the oral cavity (e.g., lysozyme), as well as the digestion processes in the stomach (e.g., exposure to low pH) and the intestine (e.g., exposure to bile). It is not clear whether strain H61 survives in animal and human intestines. It was reported that strain H61 showed weak bile tolerance in in vitro tests (Kimoto, Ohmomo, & Okamoto, 2002). However, milk can reportedly protect cells from stresses such as the conditions found in the gastrointestinal tract (Conway, Gorbach, & Goldin, 1987). It may be possible that a moderate amount of viable strain H61 in fermented milk could reach the intestines alive. On the basis of results of a self-evaluation questionnaire, a previous study indicated that H61-fermented milk decreased the incidence of

constipation and diarrhea in young women (Suzuki et al., 2013a), and the incidence of constipation decreased in the group given H61-fermented milk more (but not significantly more) than in the group given conventional yoghurt (Kimoto-Nira, Moriya, Sasaki, & Suzuki, 2015). Improvement of participants' intestinal conditions due to their intake of H61-fermented milk may contribute to the observed improvement in skin properties.

3.2.2 | Immune stimulation

The immunostimulatory activity of live cells of strain H61 has been reported in in vitro tests: strain H61 induced production of IL-6, IL-12, and tumor necrosis factor alpha (TNF- α) in a macrophage-like cell line (Kimoto et al., 2004). On the other hand, it has been reported that heat-killed cells of certain strains of *Lactococcus* did not induce production of TNF- α , although live cells did (Suzuki et al., 2008). So far, an in vivo test with live cells of strain H61 for determining immune responses has not yet been reported. Although the in vivo immune response observed in the previous study dealing with heat-killed cells may be applicable to live cells of strain H61, differences between live and heat-killed cells of strain H61 in terms of their immunostimulatory activities and effects on skin status should be investigated.

3.2.3 | Antioxidative activity

A number of studies have examined the antioxidative activity of lactic acid bacteria (Amaretti et al., 2013; Kobatake, Nakagawa, Seki, & Miyazaki, 2017; Suzuki et al., 2013b). My coworkers and I have found that live cells of strain H61 have potential superoxide dismutase activity (Kimoto-Nira, Moriya, Ohmori, & Suzuki, 2014a). In a human study (Kimoto-Nira et al., 2014b), the oxidative status of serum, as determined by a reactive oxygen metabolite test, was decreased in subjects given H61-fermented milk, as it was in subjects given conventional yoghurt; this decrease in the oxidative status of serum may be associated with the increase in skin hydration observed in both groups. On the other hand, a decrease in the oxidative index would not account for the benefit that H61-fermented milk has compared with conventional yoghurt in terms of the increase in the sebum content in the subjects' cheeks. Other oxidative indexes should be investigated after oral intake of live cells of strain H61.

3.2.4 | Other possible mechanisms

With regard to the improvement of skin status by heat-killed lactic acid bacterial cells, there are studies involving human subjects with skin troubles (Moroi et al., 2011; Yamamoto et al., 2016). The deduced mechanism underlying these beneficial effects is mainly due to improvement of an unbalanced immune response: enhancement of the host's Th1-type immune response and suppression of the over-expression of Th2-dominated responses. In contrast, there are few reports on the effect of heat-killed lactic acid bacteria on skin

health in subjects who are free of skin diseases (Kimoto-Nira et al., 2012a; Ogawa et al., 2016). Ogawa et al. (2016) reported that oral intake of heat-killed *Lactobacillus brevis* SBC8803 is effective at improving skin hydration in humans. It is also reported that oral administration of the heat-killed cells of strain SBC8803 reduces cutaneous arterial sympathetic nerve activity and increases cutaneous blood flow in rats, which are effects associated with decrease of transepidermal water loss (Horie et al., 2014). The mechanism underlying the beneficial effect of heat-killed cells of strain H61 on skin hydration observed in our previous study may be similar to this. There have also been studies on the stimulation of the nervous system by intake of lactic acid bacteria (Beppu et al., 2012; Yamano et al., 2006). It is impressive that 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one isolated from *Lactobacillus pentosus* strain S-PT84 was identified as a molecule that modulates autonomic nervous system activity (Beppu et al., 2012).

Skin health and intestinal health are closely associated. Leukotriene B₄ (LTB₄) is a bioactive lipid that plays a role in many biological processes associated with host defenses and inflammation. Since LTB₄ is associated with the pathogenesis of inflammatory bowel disease (Lobos, Sharon, & Stenson, 1987), inhibition of LTB₄ overproduction would provide an avenue for protection against inflammatory reaction. Live cells of strain H61 inhibit calcium ionophore (A23187)-stimulated LTB₄ production by a macrophage-like cell line in an in vitro test (Kimoto-Nira, Suzuki, Kobayashi, Sasaki, & Mizumachi, 2009). Heat-killed cells of strain H61 were not subjected to this test. The anti-inflammatory ability of strain H61 may support the maintenance of a healthy intestinal environment.

It is also reported that phenols (phenol and *p*-cresol) produced by intestinal bacteria can cause skin problems (Iizuka, Kawakami, & Chiba, 2009). Miyazaki, Masuoka, Kano, and Iizuka (2014) suggest that intake of certain probiotics and/or prebiotics (nondigestible food ingredients that stimulate the growth of beneficial bacteria in the colon) improves intestinal microbial balance, and thereby reduces phenol production, which is associated with maintenance of good skin condition. Mori et al. (2016) reported that intake of fermented milk containing *B. breve* strain Yakult plus galactooligosaccharides prevented dryness in human skin via beneficial effects on intestinal conditions that stimulate defecation and decrease phenol production. We did not determine phenol contents in feces from subjects administered strain H61 in any of our human studies.

The factors responsible for improved skin health following intake of strain H61 are likely to be stimulation of the immune response and the nervous system in the case of heat-killed cells and improvement of the intestinal environment and oxidative status in the case of live cells in fermented milk.

4 | PERSPECTIVES

In this review, I have introduced the beneficial effects that *Lactococcus lactis* H61 exerts on human skin health independent of the viability of the cells. With regard to live cells in fermented milk made by strain

H61, the reported effects are attractive and it is expected that consumption of H61-fermented milk will increase (Kimoto-Nira, 2014). The applications of heat-killed cells of strain H61 will likely expand further. Recently, heat-killed lactic acid bacteria with beneficial properties (*Lactobacillus paracasei* MCC1849; Maruyama et al., 2016) have become widely used in the Japanese food industry as additives for snack foods and bread. Future human studies with strain H61 to examine the beneficial effects on aging deterioration (i.e., suppression of bone density loss) are needed, which would further enhance the value of this lactic acid bacterium as an effective probiotic.

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