

## Review

# Inactivation of Foodborne Pathogens by Lactic Acid Bacteria

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**ABSTRACT** - The problems caused by foodborne pathogens are not only a concern to the food industry but also with regard to global public health. Over the years, fermentation technology has proved to be one of the cheapest and safest methods for inactivating and controlling pathogenic microorganisms in food. Scientific evidence shows that lactic acid bacteria fermentation exerts significant antimicrobial effect against pathogenic bacteria and viruses. Lactic acid bacteria metabolites such as organic acids, bacteriocins and hydrogen peroxides have adverse effects on foodborne pathogens which lead to their inhibition. These compounds do not only cause physical injuries, but also have significant effects on the pathogens' gene expression. Furthermore, the presence of lactic acid bacteria in food provides nutritional competition among foodborne pathogens, and all these factors together suppress their growth. This study reviews our current knowledge of the antimicrobial abilities of lactic acid bacteria, their molecular mechanisms, and their application for inactivating foodborne pathogens.

**Key words:** Fermentation technology, Metabolites, Antimicrobial compounds, Food safety

Foodborne pathogens and their associated diseases have always been critical to the food industry, consumers and food safety regulatory bodies globally. Of particular relevance is the recent global coronavirus (SARS-CoV-2) disease (COVID-19) pandemic which originated from a Chinese seafood market<sup>1</sup> and affected more than 30,949,804 people while killing about 959,116 people as at 22<sup>nd</sup> September 2020 (<https://covid19.who.int/>). In 1985, a *Listeria monocytogenes* serotype 4b epidemic was reported in California, USA and the outbreak was due to the consumption of contaminated Mexican-style cheese<sup>2</sup>. Also in Japan, an outbreak of a single strain of genotype GII/4 norovirus was recorded in 2006<sup>3</sup> while *Salmonella enterica* subsp. *enterica* serovar Saintpaul contaminated pepper caused an outbreak in 43 states in the United States and Canada in 2008<sup>4</sup>. Similarly in 2011, an outbreak of Shiga toxin-producing *Escherichia coli* O141:H4 was reported in Germany resulting in 3,816 infections and 54

deaths. Like the COVID-19, the disease spread from Germany to 15 other European countries and North America by travelers<sup>5</sup>. According to the Chinese National Health and Family Planning Commission on Microbial infection, at least 2,868 food safety-related incidents involving about 94,979 people were recorded in China between 2006 and 2015<sup>6</sup>. The ability of travelers to carry foodborne infections from one country to another makes global outbreaks very likely and therefore calls for global alertness when one country records an outbreak. It also calls for the use of effective food processing technologies that inactivate pathogenic microorganisms to make foods safe for consumption. One such technologies is fermentation technology. This method has been used for centuries for food processing and preservation<sup>7-9</sup>. For bacteria fermentation, lactic acid bacteria (LAB) are usually employed as the main functional strains. These bacteria are non-sporulating Gram-positive bacteria and produce lactic acid and other organic acids as they ferment carbohydrate. The fermentation process results in the metabolism of lipids and proteins into volatile compounds and some other bioactive molecules<sup>10</sup>. It has been reported that fermentation of milk proteins with *Streptococcus thermophilus* (MD2) yielded a fermentate with strong antimicrobial activity against *S. aureus*, *S. typhi* and *P. aeruginosa*<sup>11</sup>. Other LABs produce microbial peptides (bacteriocines) that inactivate many pathogenic bacteria<sup>12, 13</sup>

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suggesting that such LAB can be used in food preservation.

In this article, we review the ability of LAB to inactivate common foodborne pathogens, the mechanism(s) behind the inactivation and the potential application of LAB in the food industry for food preservation.

## Lactic acid bacteria and foodborne pathogens

Many LAB have been shown to have the potential to inhibit the growth of pathogenic bacteria that cause severe gastrointestinal diseases and severe neurological dysfunctions<sup>14,15</sup>. It is however required that LAB grow to a certain threshold before their effects on a pathogen are significantly observed<sup>16</sup>. This is because antimicrobial compounds such as bacteriocins are secondary metabolites and are produced during the stationary phase of bacteria growth phase<sup>17</sup>. Also, production of antimicrobial compounds depends on quorum sensing which is heavily dependent on cell density<sup>18</sup>. An earlier study showed that when *Lactobacillus casei* and *Listeria monocytogenes* were co-cultured in a ratio of 10:1 respectively, the populations of *Listeria monocytogenes* surpassed that of *Lactobacillus casei* when the culture was incubated at 7, 13, and 20°C. Yet, when the *Lactobacillus casei*/*Listeria monocytogenes* ratio was increased to 100:1 or 10,000:1, the growth of *Listeria monocytogenes* was significantly inhibited<sup>19</sup>. Aside bacteriocins, some LABs produce hydrogen peroxide and organic acids such as acetic acid, caproic acid, formic acid, propionic acid, butyric acid and n-valeric acid which also have bactericidal abilities<sup>20</sup>. The levels of the antimicrobial compound produced must also reach a given threshold before bacteria inactivation could be achieved as sublethal levels could make the pathogen develop cross-resistance to different stress conditions<sup>21,22</sup>. Many studies have shown the ability of LABs to inhibit the growth of *Listeria monocytogenes*<sup>23</sup>, *Staphylococcus aureus*<sup>24</sup>, *Salmonella species*<sup>25</sup>, *Escherichia coli*<sup>26</sup> and many other pathogens.

### LAB and *Listeria monocytogenes*

*Listeria monocytogenes* is a ubiquitous pathogen fairly resistant to a wide range of temperature, osmotic pressure, and pH. Its resistance depends on ecological factors and physiological conditions in the medium or substrate<sup>27</sup>. *Listeria monocytogenes* adapt to stress conditions by altering their membrane fluidity<sup>28</sup>, synthesizing sigma factors ( $\sigma^B$ )<sup>29</sup> and synthesizing osmoprotectant molecules like proline betaine, glycine betaine, acyl carnitine and carnitine<sup>30</sup>. It has been shown that the types of stress-resistance genes expressed by *L. monocytogenes* depends the type of substrate on which they grow. For instance, Miranda et al.<sup>22</sup> showed that

*L. monocytogenes* express more  $\sigma^B$  factor genes, acid resistant genes (*gadD2*), thermal resistant genes (*groEL*), and osmotolerant genes (*gbu*) when cultured in milk than when cultured in brain-heart-infusion (BHI) media. For this reason, co-culturing nisin-producing *Lactococcus lactis* DY-13 and *L. monocytogenes* in BHI significantly inhibited *L. monocytogenes* growth than when the bacteria were co-cultured in milk although high levels of nisin were produced in milk than in BHI. *Lactococcus lactis* inhibit *Listeria monocytogenes* growth by producing nisin which creates pores in the pathogen cell membrane. The bacteriocin then binds to lipid II to inhibit cell wall biosynthesis<sup>23,31</sup>. Another study showed that cheese production with a cocktail of 992 *Lactococcus lactis*, 623 *Lactobacillus rhamnosus* and 971 *Enterococcus faecium* results in the release of bacteriocin-like inhibitory substances which significantly inhibit *L. monocytogenes* growth<sup>32</sup>. Also, cheese made from raw milk containing a cocktail of *Lactobacillus brevis* 2-392, *Lactococcus plantarum* 1-399 and *Enterococcus faecalis* 1-37, *Enterococcus faecalis* 2-49, *Enterococcus faecalis* 2-388 and *Enterococcus faecalis* 1-400 inactivated *Listeria monocytogenes* when stored in various temperatures for up to 21 days<sup>32</sup>. Cheese made from pasteurized milk and ripened with the LAB cocktail however showed a bacteriostatic effect against the pathogen and this implies that milk natural microbiota also plays a role in pathogen control<sup>32</sup>. Several studies describing the use of LAB to inhibit *L. monocytogenes* growth have been summarized in Table 1.

### LAB and *Staphylococcus aureus*

According to the US Centers for Disease Control and Prevention (CDC), infections caused by *S. aureus* are ranked second among global foodborne pathogens<sup>16</sup>. The existence of methicillin-resistant *S. aureus* (MRSA) has even made the fight against the pathogen more serious and thereby attracting much scientific attention. In 2015, a staphylococcal food poisoning outbreak was reported in Umbria, Italy which affected 24 customers who ate at a restaurant<sup>33</sup>. High pathogen load and high staphylococcal enterotoxins were detected in the food samples. In the same year, the European Food Safety Authority and the European Centre for Disease Control reported 434 foodborne outbreaks among 16 of its member states<sup>34</sup>. All these reports make it imperative to apply good food processing techniques that suppress or inhibit the growth of the bacterium. Studies have shown that *Leuconostoc dextranicum* isolated from meat inhibited *S. aureus* growth when stored at 10, 15, 20, and 25°C<sup>35</sup>. Similarly, *Pediococcus cerevisiae* and *Leuconostoc citrovorum* effectively inhibited *S. aureus* growth and enterotoxin production<sup>36</sup>. The researchers reported that *S. aureus* enterotoxins were found only when the pathogen populations reached  $8 \times$

**Table 1.** Results statistics of inhibition of *Listeria monocytogenes* by LAB. Adapted from Gao et al.<sup>16</sup> with modifications

No.	Bacteria		Substance	Method	Result	Ref.
	<i>Listeria monocytogenes</i> strains	LAB				
1	211 422 506 H4 H8 4B 31C	<i>Enterococcus hirae</i> ST57ACC <i>Pediorococcus pentosaceus</i> ST65ACC <i>Lactobacillus delbrueckii</i> subsp. <i>lactis</i> NRRL B-5628	Cell free supernatant	Agar-spot test	0.13 - 0.19 cm <sup>a</sup> 0.18 - 0.22 cm <sup>a</sup> 0.7 cm <sup>a</sup> 0.8 cm <sup>a</sup> 0.7 cm <sup>a</sup> 0.7 cm <sup>a</sup>	(76)
			Cell free supernatant	Well diffusion assay	(77)	
			Suspensions	Plate count	Effect is obvious, with the increase of LAB concentration.	(19)
			Bacteriocine	Agar-spot test	Antimicrobial activity of 819,200 AU/mL	(78)
			Bacterial suspensions		200 AU/mL antimicrobial activity 400 AU/mL antimicrobial activity 1600 AU/mL antimicrobial activity 1600 AU/mL antimicrobial activity 800 AU/mL antimicrobial activity 800 AU/mL antimicrobial activity	(79)
			Cell free supernatant	Agar spot test	No effect 3 log CFU/g <sup>b</sup> 2.5 log CFU/g <sup>b</sup> 4.5 log CFU/g <sup>b</sup>	(80)
3	<i>L. monocytogenes</i> ATCC 7644	<i>Lactobacillus casei</i> 20012 pSB168 <i>Pediorococcus acidilactici</i> 13 <i>Lactococcus lactis</i> GLc03 <i>Lactococcus lactis</i> GLc05 <i>Enterococcus durans</i> GEn09 <i>Enterococcus durans</i> GEn12 <i>Enterococcus durans</i> GEn14 <i>Enterococcus durans</i> GEn17 <i>Lactobacillus curvatus</i> CWBI- B28mt <i>Lactobacillus curvatus</i> CWBI- B28wt <i>Pediorococcus acidilactici</i> H <i>Lactobacillus curvatus</i> CWBI- B28wt + <i>Pediorococcus acidilactici</i> H	Bacterial suspensions	Plate count	1.5 cm <sup>a</sup> 1.4 cm <sup>a</sup> 1.7 cm <sup>a</sup> 1.9 cm <sup>a</sup> 1.4 cm <sup>a</sup> 1.7 cm <sup>a</sup>	(81)
			Bacterial suspensions	Plate count	100% inhibition > 96% inhibition	(82)
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		
4	<i>Listeria monocytogenes</i> strains (4033 Laboratory, College of Food, Heilongjiang Bayi Agricultural University)	<i>Leuconostoc</i> ZLG3 <i>Leuconostoc</i> ZLG5 <i>Leuconostoc</i> ZLG16 <i>Leuconostoc</i> ZLG85 <i>Leuconostoc</i> ZLG93 <i>Leuconostoc</i> ZLG94	Cell free supernatant	Double agar diffusion method		
			Cell free supernatant	Double agar diffusion method		
5	V7 (serotype 1) Ohio (serotype 4b)	<i>Streptococcus thermophilus</i> (Marschall Division, Miles Laboratories, Madison, WI)	Bacterial suspensions	Surface-plated		
			Bacterial suspensions	Surface-plated		

<sup>a</sup> Diameter of bacteriostatic ring.<sup>b</sup> Decreased number of *L. monocytogenes* (CFU/g).

CFU/mL<sup>36</sup>) and this implies that the ability of LAB to suppress the growth of *S. aureus* is important to prevent disease. At a given threshold of *S. aureus* populations, the bacteria form biofilms to protect them from stress conditions<sup>37</sup>. This is achieved through quorum sensing between *S. aureus* cells. To prevent biofilm formation and suppress the growth of pathogens, the cell-to-cell communication link must be broken so as to expose the pathogens to environmental stressors<sup>38</sup>. It has been shown that *Lactobacillus fermentum* TCUESC01 (isolated from fermented cocoa) effectively inhibits *S. aureus* biofilm formation by releasing soluble molecules which suppress the expression of *icaA* and *icaR* (*S. aureus* genes involved in biofilm synthesis)<sup>24</sup>. The bacteria therefore become susceptible to effector molecules such as bacteriocines, organic acids, hydrogen peroxides and diacetyls which can cause cell death<sup>39</sup>. A similar observation was reported when *Lactococcus lactis* subsp. *lactis* biovar *diacetyllactis* inhibited the growth of *S. aureus* in milk such that no viable *S. aureus* cell was counted after 48 hours of incubation at 37°C. Cell free supernatants were found to contain organic acids and bacteriocines which caused the pathogen inactivation<sup>40</sup>. Other studies have shown that a combination of LAB strains tend to be more effective in inhibiting *S. aureus* than single strains. For instance, a cocktail of 1:1:1 ratio of *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Lactobacillus casei* var. *rhamnosus* strongly inhibited *S. aureus* NCIM 2127 better than single strains<sup>41</sup>. LABs such as *Lactococcus casei* do not only suppress the growth of *S. aureus* in food but displace them from adhering to the gut<sup>42</sup>.

### LAB and Salmonella

*Salmonella* is a common enteropathogen. Poultry is one of the commonest carriers of this pathogen although the bacterium can be present in contaminated water and foods due to unsanitary conditions. Between 19<sup>th</sup> June 2020 and 11<sup>th</sup> August 2020, about 1,012 people in 47 states in the USA had been reported by the USA Centers for Disease Control and Prevention to have been infected with *Salmonella* Newport originating from contaminated onions (<https://www.cdc.gov/salmonella/newport-07-20/index.html>). Incorporation of LAB such as *Lactobacillus amylovorus* C94 and *Lactobacillus salivarius* C86 into substrates containing *Salmonella* species has however been found to completely inactivate the pathogen even after 18 hours of inoculation<sup>25</sup>. In another study, *Lactococcus lactis* 368, *Lactobacillus curvatus* MBSa3 and *Lactobacillus sakei* MBSa1 significantly inhibited *Salmonella* biofilm formation as well as pathogen cell counts (more than six log reduction) when co-cultured<sup>43</sup>. Co-culture of *Salmonella* Typhimurium

DT104 with a cocktail of LAB (*Lactobacillus plantarum* K132, *Lactobacillus paracasei* K114 and *Lactococcus lactis* E124) resulted in complete inactivation of the pathogen. The LAB cocktail was also able to protect mice from *Salmonella* Typhimurium infection<sup>44</sup>. Even the consumption of heat-killed *Lactobacillus acidophilus* have been shown to prevent the infectivity of *Salmonella*<sup>45</sup>. Cell-free supernatants of *Weissella viridescens* WM33 and *Weissella confusa* WM36 (isolated from fermented grape) effectively inhibited *S. Typhi* and *S. Typhimurium* biofilm formation and suppressed autoinducer-2 which regulates virulent gene expression<sup>46</sup>. Other bacteria such as *Lactobacillus rhamnosus* GG produces lectin-like molecules that bind and inhibit *Salmonella* Typhimurium biofilm production<sup>47</sup>. It is known that organic acids such lactic acid, acetic acid, and citric acid produced by LABs strongly inhibit exopolysaccharide production by *Salmonella* spp<sup>48</sup>. This could be partly due to the inability of *Salmonella* to grow in low pH conditions as the optimum pH range for *Salmonella* survival is 4-9<sup>49</sup>. Also, lactic acid is known to act as a permeabilizer of Gram-negative bacteria outer membranes and this allows other compounds to enter and affect the cell<sup>26</sup>. Undissociated weak acids are lipophilic and can enter cells where they dissociate into ions to acidify the cytoplasm. These damages bacteria enzymes, inhibit protein synthesis, destroy DNA, and alter cell wall and cell membrane functions<sup>50</sup>. Several studies about the ability of lactic acid bacteria to inactivate *Salmonella* is shown in Table 2.

### LAB and *Escherichia coli*

*Escherichia coli* was formally generally considered as a non-pathogenic bacterium, till the first outbreak of enterohemorrhagic *Escherichia coli* O157:H7 was reported in the USA in 1982<sup>51,52</sup>. The bacterium is a severe human pathogen, which causes about 20,000 infections per year<sup>53</sup>. Its low infectious dose and ability to secrete Shiga toxins makes the pathogen a dangerous foodborne pathogen<sup>54-56</sup>. It has been shown that lactic acid produced by LAB is capable of disrupting the outer membrane of *Escherichia coli* making them susceptible to other environmental stressors<sup>49</sup>. For instance, *Lactobacillus agilis*, *Lactobacillus salivarius*, and *Pediococcus acidilactici* significantly prolongs the lag time and suppresses the viability of *E. coli* cells both in vitro and in gut epithelial cells<sup>57</sup>. Du et al.<sup>58</sup> also showed that supernatants of *Lactobacillus acidophilus* KLDS1.0901, KLDS1.0902 and KLDS1.1003 inhibited pathogenic *Escherichia coli* ATCC25922. Similar results were reported when cocktails of LABs were tested against *Escherichia coli*. Unlike the 1:1 ratio of LAB combinations which caused pathogenic bacteria

**Table 2.** Results statistics of inhibition of *Salmonella* by LAB. Adapted from Gao et al.<sup>(6)</sup>

Salmonella		LAB		Substance	Method	Medium	Result	Ref.
1	<i>Salmonella enterica</i> serovar Enteritidis <i>Salmonella enterica</i> serovar Typhimurium	<i>Enterococcus faecium</i> 128 <i>Enterococcus faecium</i> 131	<i>Pediococcus parvulus</i> CE11_2	Bacterial suspensions	Double agar diffusion method	MRS & TSA	0.7 <sup>a</sup> 1.2 <sup>a</sup> 1.0 <sup>a</sup> 1.15 <sup>a</sup> 1.1 <sup>a</sup> 0.975 <sup>a</sup>	(83)
2	<i>Salmonella enterica</i> serovar Typhi Ty2 <i>Salmonella enterica</i> serovar Typhimurium LT2	35 native putative probiotic Indian gut origin, 4 standard probiotic strains	<i>Lactobacillus</i> strains of	Cell free supernatant	Well diffusion assay	BHI	Antibacterial activity varies from high to low between different strains.	(84)
3	<i>Salmonella</i> Typhimurium SL1344	<i>Lactobacillus rhamnosus</i> GG (ATCC 53103)		Cell free supernatant	Plate count	MRS	8 log <sup>b</sup>	(85)
4	<i>Salmonella</i> Typhimurium ATCC 14028	<i>Lactobacillus plantarum</i> , <i>Lactobacillus bulgaricus</i> , <i>Lactobacillus helveticus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus fermentum</i>	<i>Lactobacillus rhamnosus</i> , <i>Lactobacillus helveticus</i> , <i>Lactobacillus fermentum</i>	Bacterial suspensions	Plate count	LB	<i>Lactobacillus plantarum</i> antagonistic ability of <i>Salmonella</i> generally stronger	(86)

<sup>a</sup> Diameter of bacteriostatic ring (cm).

<sup>b</sup> Decreased number of *Salmonella* (CFU/g).

**Table 3.** Results statistics of inhibition of *Escherichia coli* by LAB. Adapted from Gao et al.<sup>(6)</sup>

Escherichia coli		LAB		Substance	Method	Medium	Result	Ref.
1	<i>E. coli</i> ATCC25922 <i>E. coli</i> O157:H7 strain 35150 <i>E. coli</i> O157:H7 strain 43890 <i>E. coli</i> O157:H7 strain 43894	<i>Lactobacillus acidophilus</i> KLDLS1.0901 <i>Lactobacillus acidophilus</i> KLDLS1.0902 <i>Lactobacillus acidophilus</i> KLDLS1.1003		Cell free supernatant	Oxford cup method	LB	2.21 <sup>a</sup> 2.03 <sup>a</sup> 2.16 <sup>a</sup> 3.5 log <sup>b</sup> 3.0 log <sup>b</sup> 2.6 log <sup>b</sup> 1.1 log <sup>b</sup>	(58)
2	<i>E. coli</i> O157:H7 (from the Oklahoma State University Dairy Microbiology Laboratory)	<i>Lactobacillus lactis</i>		Bacterial suspensions	Plate count	MRS chicken meat	1.7 <sup>a</sup> 1.6 <sup>a</sup> 1.35 <sup>a</sup> 1.4 <sup>a</sup>	(87)
3	<i>E. coli</i> O157:H7	<i>Lactobacillus casei</i> <i>Lactobacillus acidophilus</i> <i>Lactobacillus helveticus</i> <i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i>		Culture supernatant	Turbidity survey	Well diffusion assay TSB	489 <sup>c</sup> 492 <sup>c</sup> 495 <sup>c</sup> 485 <sup>c</sup>	(15)
4	<i>E. coli</i> O157:H7 strain UT 10	<i>Lactobacillus plantarum</i> ATCC 8014		Bacterial suspensions	Plate count	Beef loins	The higher the cell suspension of <i>L. plantarum</i> , the earlier the onset of the inhibition of <i>E. coli</i> O157:H7.	(88)
5	<i>E. coli</i> O157:H7	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus paracasei</i> , <i>Streptococcus thermophilus</i> , <i>Lactobacillus brevis</i>		Bacterial suspensions	Plate count and oxford cup method	YPD & MRS	The best combination of inhibition: <i>L. rhamnosus</i> , <i>L. casei</i> and <i>L. plantarum</i> (3:1:3)	(59)

<sup>a</sup> Diameter of bacteriostatic ring (cm).

<sup>b</sup> Decreased number of *Escherichia coli*.

<sup>c</sup> OD value analyzed by turbidimetry method, and the OD value of *E. coli* O157:H7 pure culture is 2005 (wavelength 650 nm).

inhibition in several studies (mentioned earlier in this work), Wang et al.<sup>59)</sup> reported that the best combination ratio of *Lactobacillus rhamnosus*, *Lactobacillus casei*, and *Lactobacillus plantarum* for significant inhibition of *E. coli* O157:H7 was 3:1:3 respectively (Table 3). Although LAB metabolites may strongly affect the survival of pathogens in foods, other studies have shown that competition for nutrients and host binding sites may also play key roles also. It has been shown that in the presence of Enterohemorrhagic *Escherichia coli*, certain LABs such as *Enterococcus mundtii* CRL35 tend to increase protein expression related to carbohydrate metabolism, amino acid metabolism, transcription/translation, energy production and cell division which helps them to outgrow and suppress pathogens<sup>60)</sup>. This upregulates the expression of *Escherichia coli* genes involved in stress, energy production, and transcription while repressing genes related to amino acids and nucleotide metabolism and transport. The presence of *Enterococcus mundtii* CRL35 also causes a decrease in the adhesion capacity of *Escherichia coli* to meat extracellular matrix proteins<sup>61)</sup>.

### LAB and viruses and other pathogens

Studies regarding the use of LAB to inactivate pathogenic viruses in foods are less, but most of the studies have shown interesting outcomes. Breastmilk for example, serves a good source of nutrition for developing infants yet, serves as a medium for human immunodeficiency virus type 1 (HIV-1) transfer from breastfeeding mothers to infants. Martin et al.<sup>62)</sup> demonstrated that heat-killed *Lactobacillus* and *Pediococcus* isolated from breast milk can significantly inhibit HIV-1 infection by viruses with tropism for CXCR4 and R5/X4. This is probably because LAB may use their peptidoglycans and/or exopolysaccharide moieties to capture HIV-1 and prevent its access to infant intestine<sup>62)</sup>. This opens a door for incorporating LABs into commercial human breastmilk for infant feeding since heating would not destroy the protective activity of the LAB. Very few studies have also identified LAB metabolites with anti-viral effects. Such metabolites include Enterocin CRL35 (a cation peptide) produced by *Enterococcus faecium* CRL35 which inhibits replication of herpes simplex virus types 1 and 2 by blocking the viral late protein synthesis<sup>63)</sup>. Similarly, *Lactococcus lactis* subsp. *lactis* LM0230 growth medium filtrate significantly reduced feline calicivirus (a surrogate of human norovirus) titers and this supports the ability of LAB metabolites to inhibit pathogenic viruses<sup>64)</sup>. Different LABs may however show different abilities to inhibit viruses. Though some have been shown to inhibit viruses by their metabolites, others inhibit the pathogens competitively. For instance, cell-free supernatants of *Lactobacillus plantarum* showed antiviral effect against

Porcine epidemic diarrhea virus (a coronavirus) while live *Lactobacillus plantarum* 22F, *Lactobacillus plantarum* 25F, *Pediococcus* strains 72N and 77F reduced infectivity of the viral cells<sup>65)</sup>. Biliavska et al.<sup>66)</sup> have demonstrated that exopolysaccharides of *Lactobacillus* species may exhibit antiviral activities against Human Adenovirus Type 5<sup>66)</sup> and this reaffirms the possibility of LAB metabolites to inhibit viral growth and possible infection. The ability of LAB to inactivate viruses has largely been studied in the context of immunomodulation of the host<sup>67-69)</sup> rather than their direct effects in foods. This however shows that the presence of LAB in foods could protect consumers from viral infections by inactivating pathogens in food and also boosting the immune system to prevent viral infections after consumption. A summary of the inhibitory ability of LAB against other pathogens have been summarized in Table 4.

### Applications of the inhibitory activity of LAB to pathogens

The emphasis of food safety has always been to inactivate foodborne pathogens and to guarantee that such microbial levels are kept at lower levels that do not pose risk to human health. However, since fresh foods with the least microorganisms may not necessarily be the safest, the presence of beneficial microorganisms large enough to suppress pathogenic microbial interference may be a plausible means to keep food safe<sup>70)</sup>. For this reason, the inhibitory ability of LAB against pathogens has made them attractive in recent years in food safety. In fresh meat for instance, lactobacilli can be good preservers for inactivating *Listeria monocytogenes*, *Salmonella* Typhimurium, and *Escherichia coli* O157:H7 in beef<sup>71,72)</sup>, suppressors of *Salmonella* Typhimurium and *Escherichia coli* O157:H7 levels in pork<sup>72)</sup> and extenders of food shelf lives<sup>73)</sup>. Lactobacilli also efficiently reduce the populations of *Listeria monocytogenes* and *Salmonella* Enteritidis in chicken<sup>74)</sup> and *Salmonella enterica*<sup>75)</sup> as well as *Listeria monocytogenes* in beef sausages. Meanwhile, it is worth mentioning that, although LAB may inhibit or inactivate pathogens in foods, their fermentation activities may result in food spoilage. This therefore calls for the identification of more LAB molecules that have broad antimicrobial effects that could be used for food preservation and safety and to prevent spoilage as an unwanted side effect.

### Future perspectives

The identification of LAB metabolites in cell-free supernatants with antimicrobial activities remains interesting and holds promise for application in the food industry. Purification and identification of such molecules will enhance

**Table 4.** Results statistics of inhibition of other pathogens by LAB. Adapted from Gao et al.<sup>16)</sup>

No.	Pathogens		LAB		Substance	Method	Medium	Result	Ref.
	Bacteria		Bacteria						
1	<i>Escherichia coli</i> ATCC25922		<i>L. paracasei</i> M5-L	<i>L. rhamnosus</i> J10-L	Cell free supernatant	Well diffusion assay	TSA	+ <sup>b</sup> + <sup>b</sup> ++ <sup>b</sup> +++ <sup>b</sup>	(89)
	<i>Salmonella enterica</i> serovar Typhimurium ATCC 14028		<i>L. casei</i> Q8-L	<i>L. rhamnosus</i> ATCC 53103				+ <sup>b</sup> + <sup>b</sup> ++ <sup>b</sup> +++ <sup>b</sup>	
2	<i>Shigella sonnei</i> ATCC 25931		31 different lactobacilli (20 from curd and 11 from human milk); belonged to five species, <i>Lactobacillus casei</i> , <i>L. delbrueckii</i> , <i>L. fermentum</i> , <i>L. plantarum</i> and <i>L. pentosus</i>		Cell free supernatant	Well diffusion assay	MHA	No inhibited activity was observed Moderately inhibited by majority of CFSS Weak activity was observed Some curd isolates showed antagonism	(90)
	<i>Staphylococcus aureus</i> , <i>Listeria monocytogenes</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i>								
3	<i>Bacillus cereus</i> , <i>Salmonella enterica</i> serovar Typhi, <i>Shigella flexneri</i>								(91)
	<i>Pseudomonas aeruginosa</i> , <i>Proteus mirabilis</i>								
4	<i>Streptococcus mutans</i>								(92)
	<i>Staphylococcus aureus</i> ATCC 12600, <i>Staphylococcus epidermidis</i> 575/08, <i>Staphylococcus xylosum</i> 35/37, <i>Staphylococcus uberis</i> ATCC 700407, <i>Staphylococcus agalactiae</i> ATCC 27956, <i>E. coli</i> DSM 4230		367 wild isolates, 2 reference strains ( <i>Lactococcus lactis</i> subsp. <i>lactis</i> ATCC11454, <i>Lactobacillus rhamnosus</i> ATCC7469) and six combinations		Cell free supernatant	Well diffusion assay	MHA	170 wild isolates inhibited the growth of <i>Sc. uberis</i> , 78 <i>S. epidermidis</i> , 37 <i>S. aureus</i> , 36 <i>Streptococcus xylosum</i> , 14 <i>E. coli</i> and 13 <i>S. agalactiae</i> ; two combinations of wild strains and reference strains inhibited all six pathogens	
5	<i>Escherichia coli</i>		<i>L. acidophilus</i>	<i>L. casei</i>	Cell free supernatant	Agar diffusion test	LB	2.1 <sup>a</sup> 1.9 <sup>a</sup> 1.9 <sup>a</sup> 2.9 <sup>a</sup>	(92)
	<i>Staphylococcus aureus</i>		<i>L. bulgaricus</i> (1)	<i>L. bulgaricus</i> (2)				2.1 <sup>a</sup> 1.6 <sup>a</sup> 1.6 <sup>a</sup> 1.8 <sup>a</sup>	
	<i>Candida albicans</i>							1.2 <sup>a</sup> 1.4 <sup>a</sup> 1.1 <sup>a</sup> 1.1 <sup>a</sup>	

<sup>a</sup> Diameter of bacteriostatic ring (cm).

<sup>b</sup> Symbols refer to the size of the inhibition zone diameter observed with growing cells: +, 1 mm; ++, 2 mm; +++, 2–5 mm.

large scale chemical synthesis and commercialization for their use in large scale fermentation processes. Meanwhile the mechanisms by which such metabolites and cell components inactivate pathogens especially viruses will make it possible to identify and synthesize analogues of such biomolecules for food protection. The problems of antibiotic-resistant food-borne pathogens and the emergence of new pathogens (such as zoonotic microbes) which pose threats to human life make the search for natural antimicrobial compounds imperative. A multi-omic approach for identification, purification and characterization of LAB antimicrobial compounds combined with systems biology will be important in developing stable compounds with multifunctional abilities. In future, the application of synthetic biology coupled with multi-omics may yield multifunctional antimicrobial compounds capable of inactivation pathogenic bacteria, yeast, fungi and viruses which will be a one stop solution for numerous food industrial problems. But till then, the isolation, identification and mechanistic study of LAB (and other non-pathogenic bacteria) as well as their bioactive compounds that inactivate specific pathogens needs to be intensified.

### 국문 요약

식품 매개 병원균에 의한 문제는 식품산업뿐 아니라 세계 공공 보건에서도 문제가 된다. 최근 몇 년 간, 발효 기술은 식품 내 병원성 미생물의 불활성화 및 이를 조절하기 위한 값 싸고 안전한 방법이라는 것이 밝혀졌다. 유산균 발효는 병원성 세균 및 바이러스에 대해 유의적인 항균 효과를 갖는 과학적 증거를 보였다. 유기산, 박테리옌 및 과산화수소와 같은 유산균 대사체는 식품 매개 병원균에 대해 악영향을 미치고 이는 이들의 저해작용으로 이어진다. 이 화합물들은 물리적 결합만을 야기하는 것이 아니라 병원균의 유전자 발현에 대해서도 유의적인 저해 효과를 나타낸다. 게다가, 식품 내 유산균의 존재는 병원균에 대해 영양적인 경쟁을 제공하며 모든 요인이 그 성장을 억제한다. 본 연구는 유산균의 항균력, 분자생물학적 메커니즘 및 식품 매개 병원균의 불활성화를 위한 응용에 대하여 우리의 현 지식을 검토한다.

### Conflict of interests

The authors declare no potential conflict of interest.

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