

## Cancer Preventive Potential of Kimchi Lactic Acid Bacteria (*Weissella cibaria*, *Lactobacillus plantarum*)

REVIEW

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The number of death due to cancer has been increasing in Korea. Chemotherapy is known to cause side effects because it damages not only cancerous cells but healthy cells. Recently, attention has focused on food-derived chemopreventive and anti-tumor agents or formulations with fewer side effects. Kimchi, most popular and widely consumed in Korea, contains high levels of lactic acid bacteria and has been shown to possess chemopreventive effects. This review focuses on *Weissella cibaria* and *Lactobacillus plantarum*, the representatives of kimchi lactic acid bacteria, in terms of their abilities to prevent cancer. Further studies are needed to understand the mechanisms by which lactic acid bacteria in kimchi prevent carcinogenic processes and improve immune functions.

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**Key Words:** Kimchi, *Weissella cibaria*, *Lactobacillus plantarum*, Anticancer, Lactic acid bacteria

### INTRODUCTION

According to the Korean national statistical office, the main cause of death in Korea was cancer in 2012. The total number of deaths due to cancer in 2012 was 267,221, which was increased by 9,825 (3.8%) compared to 2011.<sup>1</sup> This was the all-time high since 1983. Currently, the treatment of cancer patients in the medical field consists mainly of surgery, radiation therapy, and chemotherapy. Seventy to eighty percent of cancer patients in chemotherapy experienced side effects such as anemia, the decreased number of white blood cells and/or platelets, oral mucositis, vomiting, diarrhea, hair loss, and disabled generative functions as chemotherapy also affects the rapidly proliferating normal cells.<sup>2</sup> Most side effects are temporary and patients recover fully; but, some side effects may take months or years to completely disappear. To decrease side effects from non-specific cytotoxicity, new drugs, such as targeted agents, are being developed to

selectively destroy specific cancer cells. However, because of problems, such as tolerance manifestation, partly critical toxicity, decrease in sensitivity, and restriction in subjects, new drugs take only a small portion of the cancer treatment realm.<sup>3</sup>

Chemoprevention is defined as the use of nontoxic or relatively safe chemical substances, such as vitamins, plant extracts, and pharmaceuticals to prevent cancer. It is effective in decreasing cancer risk and is helpful in early stages of cancer.<sup>4</sup> Hence, regular consumption of anticancer foods that display no or little toxicity to the body and boost efficacy of anti-tumor drugs or stop the development of tolerance would be beneficial in preventing cancer. Thus, consumption of plant-derived natural foods to prevent cancer with few side effects and toxicity is crucial.<sup>5</sup>

Recently, there has been a growing interest in probiotics due to the discovery of multidrug-resistant organisms that are tolerant to antibiotics. The word 'probiotics' is derived from a Greek word meaning 'for life' and holds the opposite meaning from antibio-

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tics which means 'against life'. Probiotics consist of microorganisms and substances, which modify the intestinal microflora, and when used as dietary supplement they have positive effects on health such as fortification of host immune function, suppression of diarrhea, and inhibition of carcinogenesis.<sup>6</sup>

Kimchi, a Korean traditional food, is fermented by probiotic lactic acid bacteria.<sup>7</sup> Kimchi lactic acid bacteria are known to suppress the activity of carcinogen-activating enzymes, such as azoreductase, nitroreductase, 7- $\alpha$ -dehydrogenase,  $\beta$ -glucosidase, and  $\beta$ -glucuronidase and inactivate or neutralize the cancer-causing agents and pathogenic microbes.<sup>8</sup> In addition, the intake of lactic acid bacteria as part of kimchi improves bowel movement, strengthens immunity, ameliorates hepatocirrhosis, and decreases serum cholesterol levels.<sup>9,10</sup> Among lactic acid bacteria identified during the fermentation of kimchi, *Weissella*, *Lactobacillus*, *Leuconostoc* and *Pediococcus* species are known to play an important role in kimchi fermentation.<sup>11-13</sup>

This commentary deals with anticarcinogenic effects of kimchi and lactic acid bacteria, *Weissella cibaria* and *Lactobacillus plantarum* separated from kimchi, which are known to be predominant in kimchi.

## ANTICANCER EFFECTS OF KIMCHI

Kimchi, a fermented cabbage indispensable to Korean cuisine, was once considered to be a risk factor for stomach cancer. However, unless one consumes kimchi that contains excess salt, kimchi, in general, is a healthy food recognized for its antioxidant, antiobese, cancer preventive, and other health beneficial effects.<sup>7</sup> Cancer preventive/anticarcinogenic activity of kimchi is associated with the type of ingredients and products formed during fermentation.<sup>14</sup>

The kimchi's main ingredient, Chinese cabbage, has been considered to be effective in preventing stomach cancer according to epidemiologic studies and is known to inhibit colorectal carcinogenesis due to its abundance in dietary fiber.<sup>15</sup> Garlic, in particular, has been acknowledged for its anticancer effect due to high contents of organosulfur compounds (11 to 35 mg/g). Thirty-three types of organosulfur compounds have been identified in garlic.<sup>16</sup> Organosulfur compounds in garlic have been shown to facilitate the detoxification of carcinogens by glutathione-S-transferase, modulate the activity of metabolizing enzymes such as cytochrome P450s, and inhibit the formation of DNA adducts in several target tissues.<sup>17-19</sup> Antiproliferative activity of organosulfur compounds has been demonstrated in tumor cell lines including colon, prostate, and breast, which is mediated by

induction of apoptosis via the caspase-3 signaling pathway and cell-cycle arrest.<sup>20,21</sup> One possible mechanism of cancer preventive effects of garlic in stomach cancer development involves its antimicrobial activities against *Helicobacter pylori*, a major risk factor of stomach cancer.<sup>22</sup> Hot red chili pepper powder, one of the main ingredient of kimchi, contains capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide). Although the role of capsaicin in carcinogenic processes has been controversial, there is accumulated evidence that capsaicin is capable to induce apoptosis of cancer cells by generating excess reactive oxygen species.<sup>23</sup> Thoennissen et al.<sup>24</sup> demonstrated that capsaicin caused cell-cycle arrest and apoptosis in breast cancer cells by modulating the EGFR/HER-2 pathway and inhibited the development of pre-neoplastic breast lesions by up to 80% without toxicity.

In addition to each ingredient of kimchi, kimchi extract was used to investigate cancer preventive/anticarcinogenic activity of kimchi. Extract of kimchi fermented for 3 weeks inhibited the proliferation of human cancer cell lines (gastric adenocarcinoma and acute promyelocytic leukemia). Leukemia cells treated with kimchi extract showed increased apoptosis and decreased mitochondrial transmembrane potential.<sup>25</sup> The juice of 3-week fermented kimchi suppressed the growth of K-562 human leukemia cells and MG-63 human osteosarcoma cells but no toxicity of kimchi juice was found in normal cells.<sup>26</sup>

Sarcoma180 cells transplanted mice were treated with methanol extract of 3-week fermented kimchi. Animals provided kimchi extract showed in smaller tumor weight and decreased malondialdehyde formation compared to those of the control group.<sup>27</sup>

## PROBIOTIC LACTIC ACID BACTERIA IN KIMCHI

Although there has been no general acceptance on how to define probiotic microorganisms, *Lactobacillus* species, *Bifidobacterium* sp, *Saccharomyces boulardii*, and some other microbes have been thought and used as probiotic strains.<sup>28</sup> These probiotic microorganisms have been used as food supplement in order to achieve health benefit effects of them.

There have been many studies reported on the functionality of lactic acid bacteria in the fermentation process of kimchi and their importance in the health beneficial effects of kimchi, including prevention of cancer.<sup>29</sup> According to pyrosequencing analysis of commercial kimchi samples to identify kimchi lactic acid bacteria, the genus *Weissella* was predominant at 44.4%. *W. koreensis* was 27.2% and *W. cibaria* was 8.7%.<sup>7</sup>

## 1. *Weissella cibaria*

*Weissella* is a newly separated lactic acid bacteria of lactobacillus family that was identified by a recent DNA technique. It is a Gram-positive and catalase negative bacteria included in generally recognized as safe.<sup>30</sup> The main lactic acid bacteria involved in kimchi fermentation has long been known as *Lactobacillus* genus and *Leuconostoc* genus, but more recently, *Weissella* genus lactic acid bacteria has been newly separately identified.<sup>30</sup> *Weissella* is an early dominant in kimchi fermentation and produces lactic acid, acetic acid, alcohol, dextran, and CO<sub>2</sub>, which account for the unique fresh taste and texture of kimchi.<sup>31,32</sup> *Weissella* species found in kimchi are *W. cibaria*, *W. koreensis*, and *W. hanii*.<sup>12</sup> Sources of each *Weissella* species are shown in Table 1.<sup>33</sup>

*W. cibaria*, newly named by Bjorkroth and others, has been separated from Korean kimchi and various other sources, including fermented foods, Greek salami, Spanish sausages, and animal and human excrements. *W. cibaria* is Gram-positive, non-pore formulating, non-motile, hetero lactic acid fermented, and catalase negative bacillus, and cannot produce dextran from sucrose.<sup>34,35</sup>

Studies have reported that microorganisms, including lactic acid bacteria, secreted exopolysaccharides (EPS) with the anti-cancer, anti-inflammatory, immune modulating, and blood cholesterol declining functions.<sup>36</sup> It was demonstrated that *W. cibaria*, *Leuconostoc mesenteroides* and *W. confusa* are able to produce EPS. Among these lactic acid bacteria, *W. cibaria* exhibited higher production of EPS which indicates more acid resistance (Table 2).<sup>37</sup>

*W. cibaria* was reported to have anticancer activity, immune

modulating activity, anti-inflammatory activity, and antioxidant activity. Based on the patent related to the *W. cibaria*'s anticancer activity registered by Cha et al.,<sup>38</sup> the anticancer activity in *W. cibaria* was tested with colorectal cancer cells. *W. cibaria* bacteria was incubated for 24 hours in deMan Rogosa Sharpe agar badge, diluted with phosphate buffered saline, and 10% concentration of bacteria samples were provided to normal cell strains and colorectal cancer cell strains for 72 hours. After incubation, the suppression of cell growth was measured using the MTT assay. Cell growth was suppressed by treatment of *W. cibaria* in colorectal cancer cells but not in normal cells. Ahn et al.<sup>33</sup> presented that the immune control effect of *W. cibaria* was stronger than the well-known probiotic bacterium, *L. rhammosus* GG (LGG). *W. cibaria* produced higher levels of nitric oxide, nuclear factor (NF)- $\kappa$  B, cytokines (e.g., interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ ) than LGG, suggesting that *W. cibaria* is more effective in immune control compared to LGG. Furthermore, *W. cibaria* is known to have an antiviral function against the avian influenza virus.<sup>39</sup>

Ornithine, a type of amino acid produced from its arginine precursor, is reported to accelerate growth hormone excretion and has an antiobesity effect. During the kimchi fermentation process, the level of arginine, an ornithine precursor, has decreased while the ornithine level increased rapidly, which suggested that kimchi is a source of ornithine. Moreover, a correlation between the amount of *W. cibaria* and the amount of ornithine in kimchi was observed.<sup>40</sup> Use of *W. cibaria* as a starter for food fermentation promoted the formation of ornithine from arginine, which in turn provide health beneficial effects, such as antiobesity due

**Table 1.** *Weissella* species

Species	Sources
<i>Weissella cibaria</i>	Kimchi, Malaysian foods
<i>W. beninensis</i>	Cassava fermentation
<i>W. confuse</i>	Sugar cane
<i>W. fabaria</i>	Cocoa fermentation
<i>W. ghanesis</i>	Fermented cocoa
<i>W. halotolerans</i>	Sausage
<i>W. hanii</i>	Kimchi
<i>W. hellenica</i>	Fermented Greek sausage
<i>W. kandleri</i>	Desert spring
<i>W. koreensis</i>	Kimchi
<i>W. minor</i>	Milking machine slime
<i>W. paramesenteroides</i>	Fermented Greek sausage
<i>W. salipiscis</i>	Fermented fish in Thailand
<i>W. soli</i>	Soil
<i>W. thailandensis</i>	Fermented fish in Thailand
<i>W. viridescens</i>	Cured meat products

**Table 2.** Exopolysaccharide (EPS) production of *Weissella* and *Leuconostoc* isolates from kimchi

Species	Strain No.	EPS productivity (mm) <sup>a</sup>
<i>Weissella cibaria</i>	CK0232	0.9
	CK0235	0.5
	CK0487	1.0
	CK0633	0.9
	KK0797	0.8
<i>Leuconostoc mesenteroides</i>	KK0798	0.8
	JG6054	0.7
	KM1211	0.6
<i>W. confusa</i>	CK0128	0.7
	KK0631	0.4
	KK0637	0.4

<sup>a</sup>Productivity of EPS was indicated by the diameters of slime products around colonies. The results are the average values of three replicates.

to high levels of ornithine in fermented food.<sup>41,42</sup>

## 2. *Lactobacillus plantarum*

*Lactobacillus* genus is a microorganism which does not form spores and is an anaerobic and facultative anaerobic gram-positive bacterium. This bacterium is not only widely dispersed in nature but is also found in human oral cavity and digestive organs. This bacterium is a beneficial microorganism that is widely used as a starter for various fermented dairy products.<sup>43</sup> The main kimchi lactic acid bacteria of *Lactobacillus* is *L. Plantarum*. The rapid increase of *L. plantarum* in the late stage of kimchi fermentation produces large amounts of organic acid, which is known as the main substance that acidifies kimchi. Acid tolerance of *L. plantarum* allows us to use this bacterium for natural antibacterial and antifungal products.

*L. plantarum*'s cancer preventive potential has been tested by the Ames mutation assay and the SOS chromotest. When cabbage was brined with 3% salt concentration and kimchi was fermented at 5°C for 3 weeks, kimchi extract exerted an antimutagenic effect against aflatoxin B1.<sup>44</sup> *L. plantarum*, isolated from kimchi, also exhibited a strong antimutagenic effect against *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine, 4-Nitroquinoline-1-oxide.<sup>45</sup> Furthermore, *L. Plantarum*, isolated from kimchi, had stronger antimutagenic effects compared to lactic acid bacteria originated from fermented milk.<sup>46</sup> The macrophagocytes provided with *L. plantarum* separated from kimchi strengthened phagocytosis, and displayed anticancer effects in aseites carcinoma and solid tumor due to the polysaccharide chains of muramic acid in the *L. plantarum*'s cell wall. Among lactic acid bacteria's cell wall substances, polysaccharide types rather than glycopeptide play a pivotal role in cancer suppression.<sup>47</sup>

To evaluate the possible use of *L. plantarum* as a probiotic, Lee et al.<sup>48</sup> measured the survival rate in artificial gastric fluid and intestinal fluid, adhesion compatibility with human intestinal Caco-2 cells, and antibacterial activity. As a result, *L. plantarum* strains showed more than 90% survival rate in artificial gastric fluid and intestinal fluid, and more than 400 times the survival rate of the control strain, *L. casei*. When pathogenic bacteria and lactic acid bacteria were incubated together, *L. plantarum* suppressed the adhesion of intestinal crypt cells with the pathogenic bacteria, and also suppressed pathogenic bacteria growth of *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhimurium* by 93.4%, 75.9%, and 69.3% respectively.

## CONCLUSION

This paper describes the cancer preventive/anti-carcinogenic potential of kimchi lactic acid bacteria, focusing on *W. cibaria* and *L. plantarum*. The antibiotic tolerant probiotic presented in kimchi suppresses expression of carcinogen activating enzymes and possesses many other health benefits such as suppression of growth and development of pathogenic bacteria, intestinal regulation, and immune boosts. Especially, the *W. cibaria* and *L. plantarum* found in kimchi have many effects, like anti-inflammatory, immune modulating, and blood cholesterol reducing activity, which may account for their cancer preventive/anticancer potential. These probiotic lactic acid bacteria in kimchi can not only be used as an antimicrobials in foods but also be implemented in developing functional foods to reduce the risk of colon cancer.

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## CONFLICTS OF INTEREST

No potential conflicts of interest was disclosed.

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