

PHYLOGENY AND CYTOTOXICITY SCREENING OF LACTIC ACID BACTERIA FROM CABBAGE KIMCHI SAMPLES

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ABSTRACT

Colon cancer is one of the most common and fatal cancers in the Philippines. Anticancer treatments are available but are known to produce serious side effects, showing the need for alternatives, such as those derived from natural sources. This study aimed to identify lactic acid bacteria (LAB) isolated from cabbage kimchi products sourced from the Philippines and investigate their cytotoxic activities on colorectal adenocarcinoma (HT-29), colorectal carcinoma (HCT-116), normal liver epithelial (THLE-3), and normal human neonatal dermal fibroblast (HDFn) cell lines. Phenotypic characterization and 16S rRNA gene sequencing identified the isolates as *Lactiplantibacillus plantarum* (six isolates), *Limosilactobacillus fermentum* (one isolate), and *Levilactobacillus brevis* (four isolates). Phylogenetic analysis using maximum likelihood (ML) and neighbor-joining (NJ) methods revealed close evolutionary associations among all *L. plantarum* isolates from Kimchi 1, and among all *L. brevis* isolates from Kimchi 2. At the same time, the different *L. plantarum* and *L. brevis* isolates were found to be of different strains based on the differences in their branch lengths. The *L. plantarum* isolates from K1 were shown to share a closer relationship with *L. brevis* from K2, while *L. fermentum* isolated from K1 was shown to be more distantly related to both *L. plantarum* and *L. brevis*. The secondary metabolites in the ethyl acetate extracts of the sterile culture supernatants of five LAB isolates were assayed for cytotoxic activities using the resazurin-based PrestoBlue™ reagent. Results showed that all the extracts did not produce an IC₅₀, indicating that these were not cytotoxic to the cell lines tested, in contrast to the positive control, Zeocin, which showed cytotoxicity to the different cell lines. This study provides the first insight into the LAB diversity in cabbage kimchi sourced from the Philippines and suggests the potential for further investigation of other bioactivities of these LAB isolates, particularly given their non-toxicity to the normal human cell lines THLE-3 and HDFn.

Keywords: kimchi, cancer, lactic acid bacteria, phylogenetic analysis, cytotoxicity

INTRODUCTION

In the Philippines, colon cancer ranks as the third most commonly occurring cancer for both sexes and fourth among the cancers with the highest mortality rate (Department of Health, n.d.; Philippine Council for Health Research and Development, n.d.). Anticancer treatments, such as chemotherapy and radiation, are currently available, however, they are known to cause adverse side effects. Chemotherapeutic drugs are known to target highly mitotic cells, such as the various blood cells produced in the bone marrow, resulting in anemia (Madeddu *et al.*, 2021) and weakening of the immune system (Steele, 2012); cells in the mucosal lining of the gastrointestinal tract (Akbarali *et al.*, 2022), respiratory tract (Sayit *et al.*, 2000), and cells in the hair follicles (Bodó *et al.*, 2007), among others. They have also been observed to compromise the integrity of the white matter in the prefrontal cortex, leading to cognitive impairment in 75% of chemotherapy patients (Das *et al.*, 2020). As such, alternatives that selectively target cancer cells and spare healthy tissues are becoming more essential. Active compounds isolated from bacteria have been gaining more attention due to their ubiquity and wide diversity in nature and the food industry.

Lactic acid bacteria (LAB) are Gram-positive, catalase-negative, non-spore-forming bacilli or cocci that are widely used in food production and preservation, primarily of fermented food products, due to their ability to produce lactic acid from carbohydrate sources (Zapašnik *et al.*, 2022). This group of bacteria has recently been one of the foci of anticancer research, with numerous studies showing their effectiveness against different types of cancer cell lines (Liu *et al.*, 2021). Studies have shown that the anticancer potential of lactic acid bacteria is largely mediated by LAB-derived bioactive metabolites. Compounds such as short-chain fatty acids, exopolysaccharides, and bacteriocins have been reported to exhibit cytotoxic and immunomodulatory activities that contribute to tumor growth inhibition *in vitro* and in animal models (Garbacz, 2022; Liu *et al.*, 2021). In particular, bacteriocins have been shown to disrupt cancer cell membrane integrity,

induce oxidative stress, and suppress pathways involved in tumor progression and metastasis (Niamaha *et al.*, 2024). Other mechanisms include the induction of apoptosis (Guo *et al.*, 2020) and cell cycle arrest in the G1 phase (Zhang *et al.*, 2020). These findings provide mechanistic support for evaluating the cytotoxic effects of LAB isolates from fermented food products, as performed in the present study.

Studies from South Korea (Won *et al.*, 2020; Lee *et al.*, 2016; Cho *et al.*, 2013; Jung *et al.*, 2012; Chang *et al.*, 2010), China (Ling *et al.*, 2023), Vietnam (Ong *et al.*, 2020), Indonesia (Sapalina & Retnaningrum, 2020), and Ethiopia (Gebbru & Sbhatu, 2020) isolated numerous LAB species belonging to *Lactobacillus*, *Leuconostoc*, and *Pediococcus* from kimchi, a Korean fermented vegetable product that is considered a rich source of LAB. In the Philippines, however, there are currently no published studies that explore the diversity of LAB in locally acquired kimchi. This literature gap, together with the extensive potential of LAB for anticancer activities, warranted the need for further research on the bioactivities of LAB isolated from locally fermented kimchi. The objective of this study was to establish the phylogeny of the isolated LAB and determine their cytotoxic activities on different human cancer and normal cell lines.

MATERIAL AND METHODS

Materials

Cabbage kimchi for isolation of LAB

Two packs of fermented, unpasteurized cabbage kimchi, hereafter labeled KIMCHI-1 (K1) and KIMCHI-2 (K2), were purchased from different online vendors through an e-commerce platform.

Human cell lines for cytotoxicity testing of LAB

The cytotoxic activities of the secondary metabolites of isolated LAB were tested using the following human cell lines: HT-29 colorectal adenocarcinoma, HCT-116 colorectal carcinoma, HDFn normal neonatal dermal fibroblast, and THLE-3 normal liver epithelial cell lines. The cell lines were provided by the Center for Natural Sciences and Environmental Research - Molecular Science Unit Laboratory (CENSER-MSUL) of De La Salle University-Manila, Philippines.

Isolation of LAB from cabbage kimchi samples

Procedures for the isolation of LAB from the kimchi samples were based on the study by Goa *et al.* (2022), with slight modifications. Briefly, the liquid portion of the kimchi was serially diluted with 0.9% (w/v) normal saline solution. The diluted samples were plated on Man-Rogosa-Sharpe (MRS) agar and incubated at 37 °C for 48 hours in a candle jar (~5% CO₂). Well-isolated colonies with typical LAB morphology (small to medium, white, convex, raised, with a smooth surface) were checked for purity and characterized for their Gram-stained morphology and catalase production. Gram-positive, non-spore-forming, and catalase-negative isolates were identified using 16S rRNA gene (rDNA) sequencing.

Species identification of LAB isolates and phylogenetic analysis

DNA was extracted from the isolates using a modified protocol of the Bio-Rad InstaGene™ Matrix. Endpoint PCR was carried out with a final reaction volume of 50 µL, each containing 1X PCR buffer, 1.50 mM MgCl₂, 0.30 mM dNTPs, 0.30 µM 16S rDNA forward primer 63F (5'-CAGGCCTAACACATGCAAGTC-3'), 0.30 µM 16S rDNA reverse primer 1387R (5'-CGGCGGWTGTACAAGGC-3'), 0.05 u/µL *Taq* polymerase, sddH₂O, and the DNA template. The PCR conditions were as follows: initial denaturation at 94 °C for 3 min, 35 cycles of denaturation at 94 °C for 1 min, annealing at 55 °C for 1.5 min, elongation at 72 °C for 1.5 min, and final extension at 72 °C for 5 min. Amplicons were analyzed by agarose gel electrophoresis (AGE) in 0.8% agarose gel at 50V for 90 min and viewed using a UV transilluminator. Amplicons of ~1,500 bp were sent to Apical Scientific, Malaysia for purification and sequencing. The 16S rDNA sequences of each isolate obtained using the forward and reverse primers were formed into a single contig sequence through the PRABI-Doua CAP3 Sequence Assembly Program and identified via NCBI-BLASTN with ≥98% identity considered definitive. Sequences were aligned with MUSCLE using MEGA (v. 11) for the phylogenetic analysis. Maximum Likelihood (ML) and Neighbor-Joining (NJ) phylogenetic trees were constructed using the best model from MEGA (v. 11) with a bootstrap value of 1000. Type strains for each identified species were acquired from NCBI and included in the construction of the phylogenetic tree to confirm the species identity. *Leuconostoc gasicomitatum*, a closely related LAB, and *Escherichia coli*, a distant Gram-negative bacterium, were used as the outgroups in this analysis to further verify LAB identification.

Extraction of Secondary Metabolites from LAB isolates

Out of the 11 confirmed LAB isolates, five isolates from different species and those with the highest GenBank percent identities were tested for their cytotoxic activities for the different cell lines. The protocols for the secondary metabolite extraction were adapted from Abdel-Nasser *et al.* (2023) with slight modifications, including the addition of NaCl to resolve emulsification between the aqueous and organic phases and enhance phase separation, and increasing the evaporation time instead of passing the organic phase over anhydrous sodium sulfate.

The isolates were grown in MRS broth at 35 °C for 72 hours in 5% CO₂ to support metabolite accumulation during the longer incubation period. The broth cultures were centrifuged at 9,000 x g for 10 min at 4 °C, and the supernatants were collected and filter-sterilized using 0.22 µm pore membrane filters. Multiple liquid-liquid extraction was performed by mixing the filter-sterilized supernatant with ethyl acetate at a 1:1 (v/v) ratio in a separatory funnel (Abdel-Nasser *et al.*, 2023). NaCl was added to the mixture to reduce emulsification and enhance the separation of phases. The organic phase was collected and evaporated to dryness using a rotary evaporator. The dried extracts were then resuspended to prepare 500µg/mL stock solution in 0.8% DMSO. The stock solution was filter-sterilized using 0.22 µm pore filters.

Cell Viability Assay

The cell viability assay to determine the cytotoxic activities of the LAB secondary metabolites was performed using the method of Shyu *et al.* (2014) with modifications. The cell lines HT-29, HCT-116, HDFn and THLE-3 were grown in cDMEM at 37°C with 5% CO₂ and 95% humidity to 90% confluency. The cells were harvested, and the number of viable cells/mL was determined using the trypan blue exclusion method. A minimum of 97% pre-seeding cell viability of the cell line was required before proceeding. cDMEM was used to dilute the cells to the desired viable cell density of 1 x 10⁵ cells/mL. A volume of 100 µL of the prepared inoculum was seeded into each well of the 96-well plates to result in a cell inoculum of 1 x 10⁴ cells/well. The plates were incubated for 24 hours. The spent cDMEM medium was aspirated from each well and replaced with 100 µL

aliquots of the extracts that were serially diluted two-fold in cDMEM. The plates were incubated for 72 hours under the same aforementioned conditions. Zeocin served as the positive control with the same starting concentration as the treatments, and 0.4% DMSO served as the vehicle control. Untreated cells served as the negative control. Each setup was done in triplicate.

Cell viability after treatment exposure was determined using resazurin PrestoBlue™. After incubation, the treatment solutions were aspirated from the wells. This was followed by washing with 100 µL phosphate-buffer solution (PBS) and treatment with 100 µL of 10% PrestoBlue™ in fresh cDMEM. The plates were incubated for three hours, and the optical density was read at 570 nm (for resorufin) and 600 nm (for resazurin) using the FLUOstar Omega Microplate Reader. Final absorbance values for resorufin were obtained by subtracting the absorbance values measured at 600 nm from 570 nm. The optical background of the 96-well plate, which was the average absorbance value of empty wells, was subtracted from the calculated absorbance values for resorufin. The cytotoxicity indices were calculated using the formula below and plotted against the log concentrations of the secondary metabolite extracts using GraphPad Prism™. The IC₅₀ value is the concentration that inhibits 50% of the cells. This value was determined by finding the point where the treatment concentration results in a 50% cytotoxicity index in the cytotoxicity index vs. log concentration graph.

$$\text{Cytotoxicity Index (\%)} = 100 - [(\text{OD}_{\text{final}} / \text{mean OD}_{\text{untreated}}) \times 100]$$

where,

OD_{final} optical density measurement of treated cells after wavelength and optical background subtraction

OD_{untreated} optical density of the untreated cells after wavelength and optical background subtraction

RESULTS AND DISCUSSION

Identification of LAB isolates

Figure 1 shows the colonial morphology of the isolates grown on MRS agar. Colonies showing typical LAB morphologies that were Gram-positive, non-spore forming, and catalase negative were identified using their 16S rDNA sequences. Figure 2 shows the amplicons of approximately 1.5Kb.

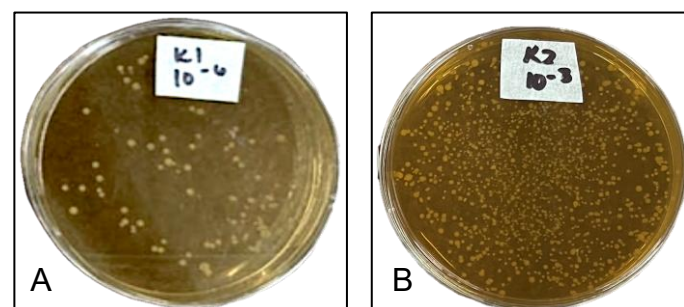


Figure 1 Colonies on MRS agar plates inoculated with ten-fold serially-diluted kimchi products after incubation at 37°C with 5% CO₂ for 48 hrs.

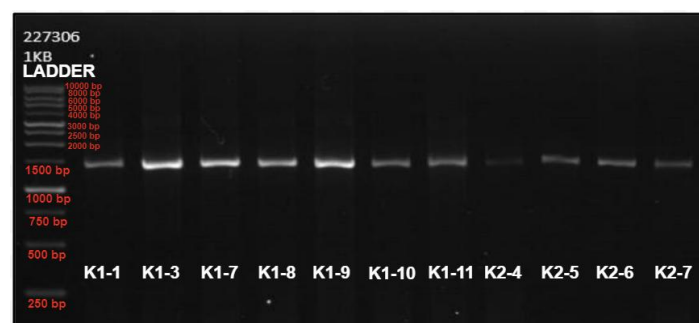


Figure 2 Purified 16S rDNA amplicons of LAB suspects from K1 kimchi and K2 kimchi in agarose after electrophoresis.

Confirmatory identification using 16S rDNA sequences

Table 1 shows the identities of the 11 isolates after BLAST analysis of the 16S rDNA sequences. All 11 isolates were identified to be LAB, with *Lactobacillus/Lactoplantibacillus plantarum* and *Lactobacillus/Limosilactobacillus fermentum* isolated from K1, and *Lactobacillus/Levilactobacillus brevis* isolated from K2. *Lactiplantibacillus plantarum* is the updated name for *Lactobacillus plantarum*, while *Levilactobacillus brevis* is the new name for *Lactobacillus brevis* (Zheng *et al.*, 2020). At the same time, the new name of *Lactobacillus fermentum* is

Limosilactobacillus fermentum. According to **Zheng et al. (2020)** and the International Scientific Association for Probiotics and Prebiotics (ISAPP) nomenclature guidelines for reclassified probiotic *Lactobacillus* species (**Sanders and Lebeer, 2020**), the abbreviated names of the isolates are as follows: *L.*

plantarum, *L. brevis*, and *L. fermentum*. Hereinafter, all isolates are referred to by their more updated names, while the abbreviated genus names remain unchanged. It is noted that the high percent identity of these results implies that the identities of the species based on the nucleotide sequences are highly reliable (Table 1).

Table 1 Identities of the isolates from K1 kimchi and K2 kimchi and their respective GenBank % ID. The entries in the indicated NCBI accession numbers contain the complete 16S rDNA sequences.

Isolate	Species	GenBank % ID	Accession Number
K1-1	<i>Lactobacillus plantarum</i> ^a	99.53%	PP491061
K1-3	<i>Lactobacillus plantarum</i> ^a	99.62%	PP491062
K1-7	<i>Lactobacillus plantarum</i> ^a	99.69%	PP491063
K1-8	<i>Lactiplantibacillus plantarum</i>	99.76%	PP491064
K1-9	<i>Lactobacillus plantarum</i> ^a	99.54%	PP491065
K1-10	<i>Lactiplantibacillus plantarum</i>	99.77%	PP491066
K1-11	<i>Lactobacillus fermentum</i> ^b	99.92%	PP491067
K2-4	<i>Lactobacillus brevis</i> ^c	99.69%	PP491068
K2-5	<i>Lactobacillus brevis</i> ^c	99.85%	PP491069
K2-6	<i>Lactobacillus brevis</i> ^c	99.53%	PP491070
K2-7	<i>Levilactobacillus brevis</i>	99.16%	PP491071

^a updated name is *Lactiplantibacillus plantarum*

^b updated name is *Limosilactobacillus fermentum*

^c updated name is *Levilactobacillus brevis*

The common genera isolated from kimchi products include *Leuconostoc*, *Weisella*, and *Lactobacillus* (**Noh et al., 2016**). Based on the NCBI BLAST analysis, the identified isolates in this study all belonged to the genus *Lactiplantibacillus*, *Limosilactobacillus*, and *Levilactobacillus*, which were all previously classified under the genus *Lactobacillus*. Six (6) isolates from K1 were identified to be *L. plantarum*, while one was identified as *L. fermentum*. The four (4) isolates from K2 were identified to be *L. brevis*. The results are consistent with the findings of **Kwon et al. (2014)**, who reported that the primary drivers for kimchi fermentation are *L. plantarum* (predominant in K1), *L. brevis* (predominant in K2), *Leuconostoc pseudomesenteroides*, *Leuconostoc lactis*, and *Leuconostoc mesenteroides*. They

also noted that the pH changes resulting in an acidic environment (pH of 4) during the fermentation process of kimchi production could favor the predominance of certain LAB species, particularly *L. plantarum*. With that said, the predominance of *L. plantarum* in K1 might suggest that the K1 sample has been fermented longer and was more acidic than K2, causing a difference in the LAB constitution observed in both samples. The same species identified in this study were also isolated from kimchi samples that were mostly sourced from South Korea (**Won et al., 2020; Lee et al., 2016; Cho et al., 2013; Jung et al., 2012; Chang et al., 2010**).

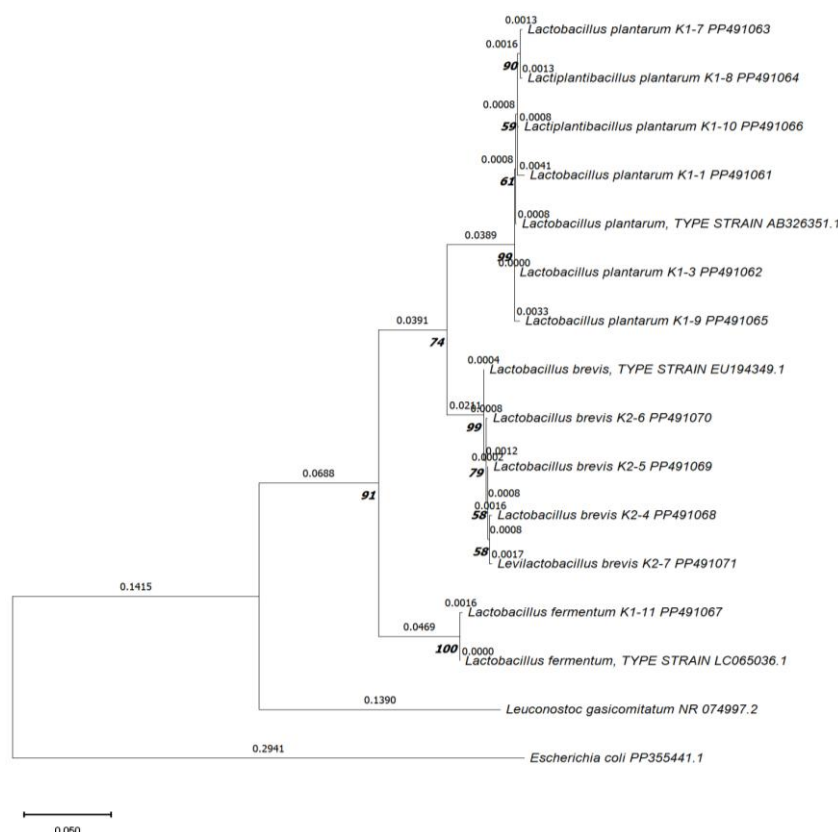


Figure 4 The Maximum Likelihood (ML) phylogenetic tree of the 11 LAB isolates from K1 kimchi and K2 kimchi based on their 16S rDNA sequences with type strains for each identified species and two outgroup species, namely *Leuconostoc gasicomitatum* and *Escherichia coli*.

During kimchi fermentation, microbial succession occurs as changes in pH progressively alter the kimchi microbial ecosystem toward more anaerobic and acidic conditions (**Kwon et al., 2014; Jung et al., 2014; Chang et al., 2010; Lee et al., 2015**). Therefore, LAB species that differ in acid tolerance and acid production capacity may predominate at different stages of fermentation. For example, *Leuconostoc* species, such as *L. mesenteroides*, dominate the early

fermentation period under relatively less acidic conditions, whereas as the pH continues to decrease over time (from approximately pH 6 to pH 4) due to the accumulation of lactic acid and other organic acids, other LAB species such as *L. plantarum* increase in abundance during the later stages of fermentation due to higher acid tolerance (**Jung et al., 2014; Lee et al., 2015; Jung & Lee, 2020**). *L. plantarum*, a facultative heterofermenter, primarily metabolizes hexoses by

glycolysis to produce lactic acid, and under low hexose availability can generate lactate and acetate end products from pentoses via the phosphoketolase pathway (Mullan, 2014). In contrast, *L. brevis* and *L. fermentum*, as obligate heterofermenters, use the phosphoketolase pathway to metabolize hexoses and produce mixed fermentation end products. While these LAB species possess acid tolerance (Gebru & Sbhatu, 2020; Lim et al., 2020; Kim et al., 2021), their metabolic differences may explain why *L. plantarum* confers a competitive advantage over other LAB species through greater metabolic flexibility and fermentation efficiency, contributing to its predominance in the K1 sample. A thorough literature search showed that, in the Philippine setting, there are currently no published studies that isolated LAB from locally sourced cabbage

kimchi, implying that this study might be the first to characterize the LAB diversity in locally sourced cabbage kimchi.

Phylogeny of the Isolated LAB

The 16S rDNA sequences of the isolates were used to construct a Maximum Likelihood (ML) (Fig. 4) and a Neighbor-Joining (NJ) (Fig. 5) phylogenetic trees to determine the evolutionary relationship among the species isolated from K1 and K2 (Table 2).

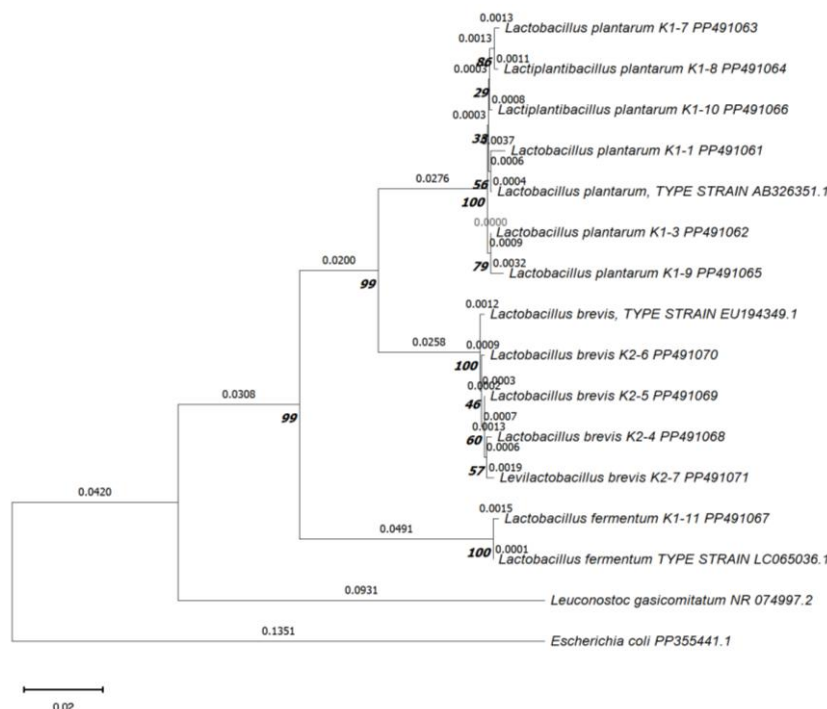


Figure 5 The Neighbor-Joining (NJ) phylogenetic tree of the 11 LAB isolates from K1 kimchi and K2 kimchi based on their 16S rDNA sequences with type strains for each identified species and two outgroup species, namely *Leuconostoc gasicomitatum* and *Escherichia coli*.

According to Zou et al. (2024), phylogenetic trees mainly consist of two methods: (1) distance-based methods (e.g. NJ) and (2) character-based methods (e.g. ML). Finding the similarities between the two phylogenetic trees strengthens the evidence for species relatedness. Phylogenetic analysis shows that all isolates were grouped together with the type strain of their respective species (Fig. 4 & 5), reinforcing their species identification in Table 1. Furthermore, analyzing the branch lengths reveals that the six (6) isolates of *L. plantarum* from K1 are of different strains. This is also true for the four (4) isolates of *L. brevis* from K2. The branch distances are different for the isolates belonging to the same species, indicating that there are nucleotide differences that separate the different isolates of the same species from each other. In addition, the same pattern was observed in both ML and NJ phylogenetic trees, wherein *L. plantarum* from K1 appears to share a closer relationship with *L. brevis* from K2 since they share a common ancestor. On the other hand, *L. fermentum* isolated from K1 appears to be more distantly related to both *L. plantarum* and *L. brevis*. All the isolates are assumed to have evolved from a common ancestor that is more closely related to *Leu. gasicomitatum* than *E. coli*, further strengthening the classification of the isolates in Table 1 as LAB. Phylogenetic trees from Zhang et al. (2011) and Kaur et al. (2017) have also observed a similar relationship between *L. fermentum*, *L. plantarum*, and *L. brevis*.

Cell Viability Assay

The confluency of the HDFn, THLE-3, HT-29, and HCT-116 cells grown in cDMEM was first checked prior to the seeding of the 96-well plates for the cytotoxicity assay. At least 90% cell confluency is considered optimum to reach the desired seeding density of 1×10^5 cells/mL with a minimal volume of the cells. Figure 7 shows the HT-29 cell line, pre-trypsinization with cell confluency of at least 90%. This was determined by comparing the field-of-view coverage of the adherent cells versus the empty space between the cells. In Figure 7, only minimal spaces between the cells can be observed, indicating high confluency.

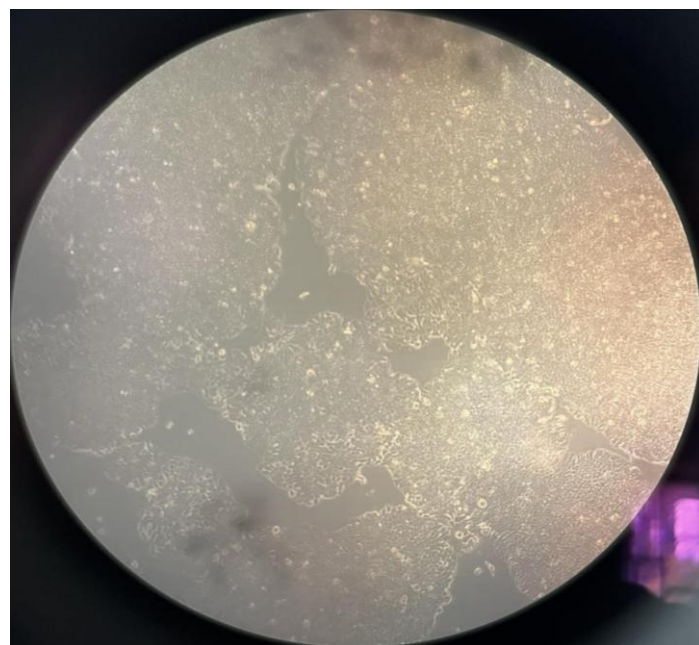


Figure 7 HT-29 cell line showing an example of a >90% confluency, which is one of the criteria for seeding into the 96-well plates for the cytotoxicity assay.

The corrected absorbance readings at 570 nm (absorbance at 570 nm less absorbance at 600 nm) taken after the treatment of the set-ups with PrestoBlue™ were used to compute the cytotoxicity indices of the different LAB extracts, zeocin, and 0.4% DMSO for the different cell lines. and analyzed using GraphPad Prism™. Figure 8A-D shows that the highest concentrations of the extracts tested did not produce the IC₅₀, i.e. the concentration that inhibits 50% of the cells tested. In comparison, zeocin showed cytotoxic activity against the different cell lines.

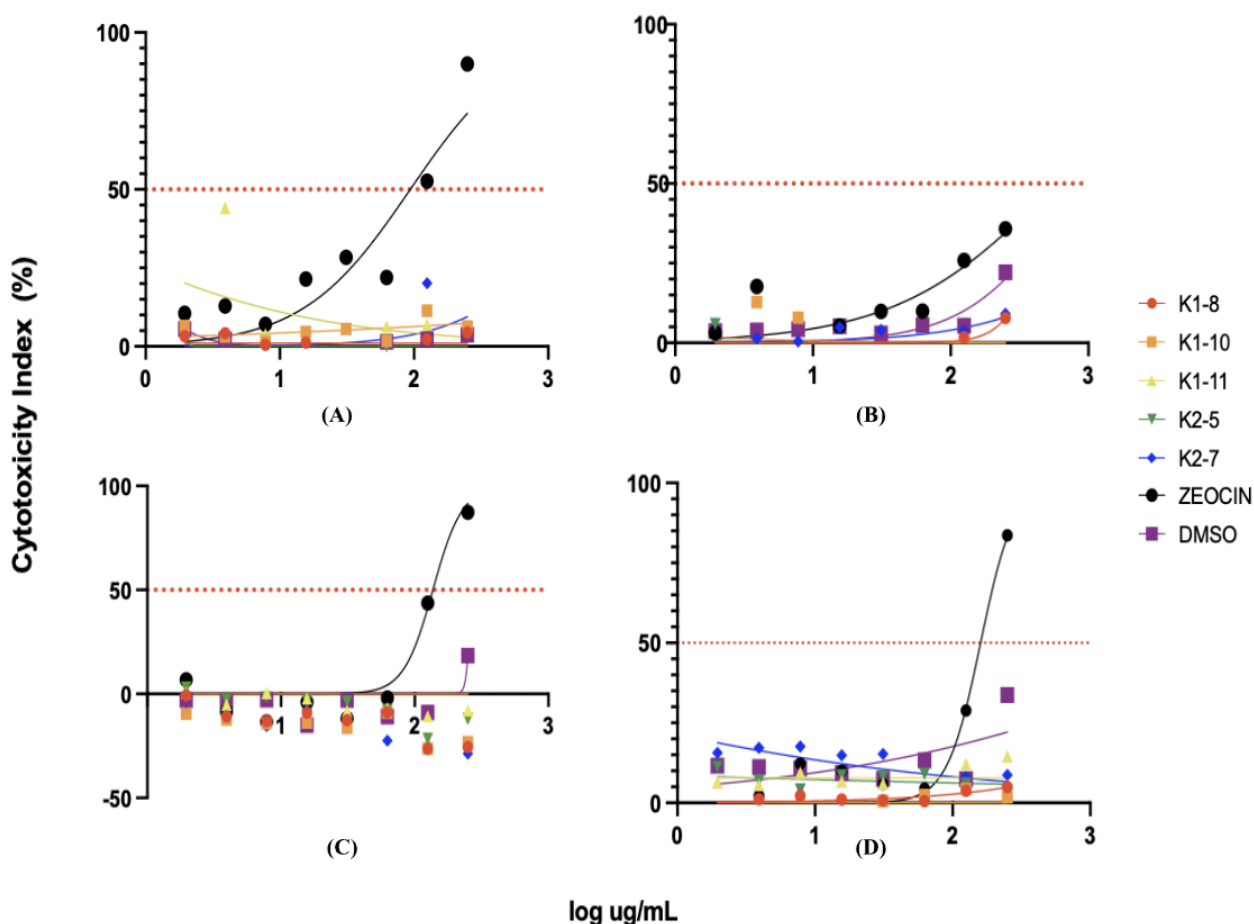


Figure 8 Dose-response non-linear regression analysis of the cytotoxicity indices (% CI) of ethyl acetate extracts of sterile culture supernatants from lactic acid bacteria isolated from K1 kimchi and K2 kimchi, zeocin, and 0.4% DMSO for (A) HDFn, (B) THLE-3, (C) HT-29, and (D) HCT-116 after 72 hours of treatment.

The absence of cytotoxic activities of the extracts from the different LAB isolates is in contrast to the findings of Shyu *et al.* (2014), who tested the cytotoxic activity of lactobacilli from Philippine commercial dairy products on HCT-116, HT-29, and HDFn. In their study, metabolites from the lactobacilli were found to be significantly cytotoxic to the HCT-116 and HT-29 cell lines, but not to the normal HDFn cell line. The results may be due to the inherent intraspecies and interspecies differences of *Lactobacillus* spp., especially if these are isolated from different sources. Lactobacilli of the same species but of different strains can exhibit variations in their bioactivities, leading to a difference in the composition of their secondary metabolites, affecting their potential for cytotoxic activity on different cell lines.

In the study by Shyu *et al.* (2014), the secondary metabolites were found to upregulate the early apoptotic gene markers, *cfos* and *cjun*. These gene markers produce protein products that form the AP-1 transcription factor, which promotes apoptosis through the mitogen-activated protein kinase (MAPK) and tumor necrosis factor related apoptosis inducing ligand (TRAIL) pathways, suggesting a potential mechanism for the cytotoxic activity of the isolated *Lactobacillus* spp. In a study by Zhao *et al.* (2024), the secondary metabolites of *Lactobacillus plantarum* isolated from traditionally fermented products were found to inhibit the proliferation of HT-29 cells, possibly through the p38 MAPK pathway, which is important in cell differentiation, transformation, and apoptosis. Furthermore, identification of the chemical profile of the secondary metabolites revealed that 2'-deoxyinosine was the main anti-colorectal cancer substance and primarily blocks the growth of cancer cells in the S phase. A review by Zhong *et al.* (2014) also highlights the antitumorigenic activity of *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* on HT-29 cells through the production of exopolysaccharides, which induce Beclin-1 and GRP78, leading to autophagy. The mixture of different compounds in the crude extract that was tested may also exhibit antagonistic effects on the bioactive components, leading to the absence of cytotoxic activity (Caesar & Cech, 2019). The results do not discount the presence of other bioactivities that were not tested in the study.

CONCLUSION

The study identified LAB isolated from two local cabbage kimchi products and assessed their cytotoxic activities on cancer and normal cell lines. The findings revealed that the highest concentrations (250 µg/mL) of the ethyl acetate extracts of the sterile culture supernatants from five LAB isolates tested (identified as

Lactiplantibacillus plantarum, *Limosilactobacillus fermentum*, and *Levilactobacillus brevis*) did not produce an IC₅₀, showing the absence of cytotoxic activities for the HT-29, HCT-116, HDFn and THLE-3 cell lines.

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