Cytotoxicity of *Lactobacillus plantarum* KK518 Isolated from Pak-Sian Dong (Thai Fermented Gynandropsis pentaphylla DC.) Against HepG2, MCF-7 and HeLa Cancer Cells

Vijitra Luang-In1,*, Worachat Saengha1, Benjaporn Buranrat2, Sutisa Nudmamud-Thanoi3, Arjan Narbad4, Supaporn Pumriw5, Wannee Samappito6

ABSTRACT

**Background:** Pak-Sian Dong is a fermented vegetable product of Thailand prepared from aerial parts of Pak-Sian (*Gynandropsis pentaphylla* DC.). *Lactobacillus plantarum* KK518 was isolated from Pak-Sian Dong and already assessed for its probiotic attributes. **Objective:** The aim of this work was to determine the untapped cytotoxic effects of *L. plantarum* KK518 extract against HepG2 (liver cancer), MCF-7 (breast cancer) and HeLa (cervical cancer) cells. **Materials and Methods:** The bacterial extracts were prepared from whole cultures; containing cells and broth using ethyl acetate as extracting solvent and the dried extracts were redissolved in ethanol before use. Cytotoxic, antiproliferative and antimigratory effects of the bacterial extracts on three types of cancer cells were determined using 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) assay, clonogenic formation and wound healing assays, respectively. **Results:** *L. plantarum* KK518 extract showed the highest cytotoxicity at 90.88% at 1,000 µg/mL against HeLa cells (IC50 of 371.97 µg/mL) over 48 h of exposure. Anti-colony formation test showed that the bacterial extracts at 600, 800 and 1,000 µg/mL over 48 h led to a complete inhibition of colony formation of HeLa cells; however the highest IC50 of 418.52 µg/mL was found in HepG2 cells suggesting that HepG2 was least affected by bacterial extract. Likewise, HepG2 cells seemed to be most resistant to antimigratory effects as observed by highest relative area of the wound at most time intervals and most extract concentrations. **Conclusion:** *L. plantarum* KK518 offers a potential use as a bio-therapeutic with chemopreventive effects against cervical, breast and liver cancers. **Key words:** HepG2, HeLa, MCF-7, *L. plantarum* KK518, Pak-Sian-Dong.

INTRODUCTION

Cancer is the most common cause of death in Thailand, with 85,000 fatalities a year from liver and bladder, lung, colon, breast and cervical disease. Over the next 21 years, 24 million Thais are predicted to be diagnosed with cancer.1 Chemotherapy is one of the most effective treatments for prolonging the patient's life. However, many chemotherapeutic drugs encountered reduction of therapeutic effect due to the problem of drug-resistance2 and may as well exert toxicity to normal cells leading to unpleasant side effects to the patients. These adverse sides of cancer chemotherapy prompt the continuing discovery of novel anticancer agents or alternative treatments. Microbes have so far established their candidacy as alternative anticancer treatment through the production of several bioactive compounds such as antioxidant enzymes, immune toxins, proteins, and secondary metabolites for therapeutic purposes.3 Certain fermented foods have been linked to anticancer benefits due to bioactive natural products from vegetables and also lactic acid bacteria (LAB). For example, kimchi, a fermented cabbage originated from Korea, has been well-recognized for its antioxidant, antiobese, cancer preventive, and other health-promoting benefits.4 The functionality of LAB mainly from the predominant genus *Weissella* followed by *Lactobacillus plantarum* in the fermentation process of kimchi also contributed to its cancer prevention.5 In Thailand, Pak-Sian-Dong is a fermented vegetable product prepared from aerial parts of Pak-Sian (*Gynandropsis pentaphylla* DC.) and it has been commonly consumed in Northeastern Thailand. LAB namely *Pediococcus cerevisiae*, *Lactobacillus brevis* and *Lactobacillus plantarum* have been major species prevalent during fermentation of Pak-Sian-Dong.6 The previous work showed probiotic attributes of *Lactobacillus plantarum* KK518 isolated from Pak-Sian Dong in Khon Kaen province, Thailand.7 However, its cytotoxic effect is yet to be evaluated. *L. plantarum* has been well-known for prominent probiotic effects documented extensively for rats, poultry and pigs.8 In spite of the emerging evidence of anticancer attributes of LAB, very limited data is available on cytotoxic and antiproliferative activity of *L. plantarum*. Therefore, the aim of this work was to determine the cytotoxicity of *L. plantarum*...
PBS buffer (pH 7.2) was added to the wells and incubated at 37 °C under 48 h. Crude microbial extracts (0, 400, 600, 800 and 1,000 µg/mL) were

Xenon, China).

the cell colonies were counted using inverted microscope (NIB-9000, with 0.25% Trypsin-EDTA. DMEM media were added to cell lines and

with phosphate-buffered saline (PBS), pH 7.2 before trypsinization

Cytotoxicity was measured using MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide)(Sigma, USA) assay following the

method.\(^9\) MCF-7, HeLa and HepG2 cells (5×10^3 cells/mL) were pipetted into 96-well plates and incubated at 37 °C under 5% CO\(_2\), DMEM media for cell lines cultures were renewed every 2-3 days until 80% confluency was reached. Cultured cell lines were washed with phosphate-buffered saline (PBS), pH 7.2 before trypsinization with 0.25% Trypsin-EDTA. DMEM media were added to cell lines and the cell colonies were counted using inverted microscope (NIB-9000, Xenon, China).

Cytotoxicity assay

Cytotoxicity was measured using MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide)(Sigma, USA) assay following the method.\(^9\) MCF-7, HeLa and HepG2 cells (5×10^3 cells/mL) were pipetted into 96-well plates and incubated at 37 °C under 5% CO\(_2\) for 48 h. Crude microbial extracts (0, 400, 600, 800 and 1,000 µg/mL) were added to wells and incubated for 48 h. MTT (5 mg/mL) dissolved in PBS buffer (pH 7.2) was added to the wells and incubated at 37 °C under 5% CO\(_2\) for 4 h. MTT was removed and 200 µL DMSO was added to dissolve the formazan and the purple color appeared if cells were alive. The absorbance was measured at 590 nm using microplate reader (M96S+, Mastertech, Taiwan). Cytotoxicity of crude microbial extracts against cancer cells was measured as IC\(_{50}\) value. When % cytotoxicity was ≤ 50%, it represented non-cytotoxic effect and when % cytotoxicity was >50%, it represented cytotoxic effect. Cell morphology was also observed using an inverted microscope (NIB-100, Xenon, China).

Clonogenic assay

The colony formation assay was used to evaluate the effect of crude microbial extract on the regrowth of cancer cells as previously described.\(^3\) The viable cancer cells were seeded in 6-well plates at a concentration of 500 cells/well for 24 h. The cells were then treated with various concentrations of crude microbial extracts (0, 400, 600, 800 and 1,000 µg/mL) for 24 h. Subsequently, the cells were washed with PBS buffer and resuspended into fresh DMEM and grown for 24 days. Subsequently, the DMEM medium was discarded, the cells were washed with PBS buffer three times, fixed with 100% methanol at −20°C, stained with 0.5% crystal violet in 100% methanol for 1 h at room temperature, washed with tap water, and the colonies were viewed and captured using a digital camera (Nikon D50).

Wound healing assay

Cell migration was evaluate using a wound healing assay as previously described.\(^4\) Briefly, cancer cells were seeded into 24-well plates for 24 h. Cells were scratched using a sterile 0.2-µL pipette tip, certain cells were untreated and others were treated with different concentrations of crude microbial extracts (0, 400, 600, 800 and 1,000 µg/mL). Images were obtained from 0 to 48 h. The relative area (%) of the scratch = area of scratch at T h(area of scratch at 0 h x 100. Cell migration was monitored by phase contrast microscopy (NIB-9000 inverted microscope; magnification, ×10, Xenon, China).

Statistical analysis of data

Data were collected in triplicate and results were reported as means ± standard deviation (SD). Statistical analysis was performed using One-way analysis of variance (ANOVA) and Duncan multiple range’s test by the software SPSS (demo version). Statistically significant differences were considered if \(p < 0.05\).

RESULTS

Cytotoxicity of L. plantarum KK518 extract on cancer cells

It was found that L. plantarum KK518 extract had cytotoxic effects on three types of cancer cells; HepG2, MCF-7 and HeLa cells in a dose-dependent manner (Table 1). The greatest antiproliferative effect on all cancer cells was observed at the highest dose (1000 µg/mL) of the bacterial extract. It seems L. plantarum KK518 extract was least cytotoxic towards MCF-7 cells based on the lowest cytotoxicity percentage at 68.53% at 1000 µg/mL bacterial extract and most cytotoxic towards HeLa cells at 90.88% at 100 µg/mL bacterial extract (Table 1). These results were in accordance with the calculated IC\(_{50}\) values of L. plantarum KK518 extract on cancer cells. The inhibition concentration of 50% growth (IC\(_{50}\)) was determined. It was shown that the lowest IC\(_{50}\) values was derived from HeLa cells (Table 1) at 371.97 µg/mL.

Table 1: Cytotoxicity of Lactobacillus plantarum KK518 extract on cancer cells over 48 h of exposure.

<table>
<thead>
<tr>
<th>Concentration (µg/mL)</th>
<th>HepG2 (\text{IC}_{50}) (µg/mL)</th>
<th>HeLa (\text{IC}_{50}) (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>90.00 ± 0.31(^a)</td>
<td>68.53 ± 1.03(^a)</td>
</tr>
<tr>
<td>800</td>
<td>70.00 ± 4.86(^b)</td>
<td>63.10 ± 9.15(^c)</td>
</tr>
<tr>
<td>600</td>
<td>27.05 ± 1.39(^c)</td>
<td>42.67 ± 7.37(^b)</td>
</tr>
<tr>
<td>400</td>
<td>20.00 ± 6.02(^a)</td>
<td>28.21 ± 1.06(^a)</td>
</tr>
<tr>
<td>(\text{IC}_{50}) (µg/mL)</td>
<td>661.45 ± 0.80(^a)</td>
<td>682.53 ± 0.67(^a)</td>
</tr>
</tbody>
</table>

Small letter and capital letter superscripts indicate significant differences (\(p < 0.05\)) in the columns and rows, respectively.
µg/mL and the highest IC₅₀ value was from MCF-7 cells at 682.53 µg/mL (Table 1). No cytotoxicity activity was detected for MRS medium as a negative control against three types of cancer cell lines in this study (results not shown).

Apoptosis in cancer cells

Apoptosis is an autonomous process involving the activation, expression, and regulation of a number of genes, which leads to programmed cell death to rid of unwanted or abnormal cells in organisms and maintain a stable internal environment. The changes in cell morphology induced by *L. plantarum* KK518 extract treatment at 1000 µg/mL for 48 h under a phase contrast microscope were examined for the preliminary characterization of the cytotoxicity induced by the bacterial extract the cancer cells. In all treated cancer cell lines by bacterial extracts, cell rounding up, cell shrinkage, membrane blebbing and lack of cell adhesion were observed (Figure 1) as opposed to non-treated cancer cells. This indicated that *L. plantarum* KK518 extract in this work was able to induce apoptosis resulting in cancer cell death as observed by apoptotic bodies (Figure 1).

Anti-colony formation effect

In addition to the cytotoxicity effect, the antiproliferative effect of microbial extracts on long-term viability of cancer cells was investigated using a colony formation assay. The results showed that bacterial extracts from *L. plantarum* KK518 led to a dose-dependent decrease in the colony forming capacity of HepG2, MCF-7 and HeLa cells with IC₅₀ values (Table 2; Figure 2) lower than those found in cytotoxicity effect to induce cancer cell death (Table 1), except for HeLa cells that its IC₅₀ value was not determined since bacterial extract concentrations at 600, 800 and 1,000 µg/mL led to a complete inhibition of colony formation. Thus, HeLa cells are the most sensitive to bacterial extracts whilst HepG2 was most resistant due to the highest IC₅₀ value of 418.52 µg/mL. To sum up, lower concentrations of bacterial extracts suffice to exert the antiproliferative effect in a longer time (24 days) in clonogenic assay when compared to the cytotoxic effect in a shorter time (48 h).

Antimigratory effect

Next, antimigratory effects of *L. plantarum* KK518 extracts on cancer cells were also examined. The results demonstrate that the bacterial extract inhibited cancer cell migration by decreasing wound-healing capacity in a dose-dependent manner in all three cancer cells (Table 3; Figure 3). However, HepG2 cells seemed to be most resistant to antimigratory effects caused by *L. plantarum* KK518 extracts as observed by highest relative area of the wound at most time intervals and most concentrations (Table 3). HeLa cells were most sensitive to the bacterial extract at 12 h and 24 h.

![Figure 1: Cell morphology of HepG2, MCF-7 and HeLa cells after treatment with 1000 µg/mL of *L. plantarum* KK518 extract over 48 h of exposure compared to the untreated cells. White arrows point to live cells and red arrows point to dead cells.](image-url)

![Table 2: Anti-colony formation of *L. plantarum* KK518 extract on cancer cells.](table-url)

<table>
<thead>
<tr>
<th>Concentration (µg/mL) of <em>L. plantarum</em> KK518</th>
<th>Colony formation (% of control)</th>
<th>IC₅₀ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HepG2</td>
<td>MCF-7</td>
</tr>
<tr>
<td>0</td>
<td>100.00 ± 0.00⁸⁷,a</td>
<td>100.00 ± 0.00⁸⁷,a</td>
</tr>
<tr>
<td>400</td>
<td>48.14 ± 0.53⁸⁴,b</td>
<td>14.46 ± 0.21⁸⁴,b</td>
</tr>
<tr>
<td>600</td>
<td>27.99 ± 1.57⁸⁵,c</td>
<td>12.25 ± 0.33⁸⁵,b</td>
</tr>
<tr>
<td>800</td>
<td>11.94 ± 1.06⁸⁶,c</td>
<td>5.56 ± 0.32⁸⁶,b</td>
</tr>
<tr>
<td>1000</td>
<td>8.21 ± 1.06⁸⁶,c</td>
<td>1.30 ± 0.32⁸⁶,b</td>
</tr>
</tbody>
</table>

Small letter and capital letter superscripts indicate significant differences (p < 0.05) in the columns and rows, respectively. ND = Not determined.

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Table 3: Wound healing effect of L. plantarum KK518 extract on cancer cells.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Concentration (µg/mL) of L. plantarum KK518</th>
<th>0 h</th>
<th>12 h</th>
<th>24 h</th>
<th>36 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepG2</td>
<td>0</td>
<td>100 ± 0.00^a</td>
<td>98.73 ± 1.34^a</td>
<td>74.80 ± 0.28^c</td>
<td>65.70 ± 0.84^d</td>
<td>0.00 ± 0.00^e</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>100 ± 0.00^a</td>
<td>98.26 ± 0.81^a</td>
<td>84.50 ± 0.26^c</td>
<td>79.90 ± 1.13^d</td>
<td>52.59 ± 0.98^f</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>100 ± 0.00^a</td>
<td>98.76 ± 1.35^a</td>
<td>84.98 ± 0.02^h</td>
<td>83.55 ± 1.48^A</td>
<td>58.00 ± 0.78^A</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>100 ± 0.00^a</td>
<td>99.53 ± 0.55^a</td>
<td>97.97 ± 0.95^c</td>
<td>87.65 ± 3.60^B</td>
<td>82.02 ± 0.42^C</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>100 ± 0.00^a</td>
<td>99.35 ± 0.54^a</td>
<td>98.89 ± 0.45^dA</td>
<td>90.95 ± 10.6^B</td>
<td>91.80 ± 0.85^A</td>
</tr>
<tr>
<td>MCF-7</td>
<td>0</td>
<td>100 ± 0.00^a</td>
<td>80.46 ± 0.64^bA</td>
<td>68.10 ± 1.83^c</td>
<td>43.39 ± 1.77^d</td>
<td>0.00 ± 0.13^d</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>100 ± 0.00^a</td>
<td>82.32 ± 0.00^a</td>
<td>72.93 ± 0.16^c</td>
<td>56.08 ± 0.04^E</td>
<td>49.28 ± 0.61^A</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>100 ± 0.00^a</td>
<td>82.58 ± 0.08^A</td>
<td>77.78 ± 0.13^bA</td>
<td>71.89 ± 0.09^A</td>
<td>64.46 ± 0.04^A</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>100 ± 0.00^a</td>
<td>95.85 ± 0.08^bA</td>
<td>95.50 ± 0.07^c</td>
<td>95.58 ± 0.09^A</td>
<td>95.42 ± 0.04^C</td>
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<td></td>
<td>1000</td>
<td>100 ± 0.00^a</td>
<td>99.21 ± 0.09^dA</td>
<td>99.25 ± 0.05^b</td>
<td>99.25 ± 0.04^dA</td>
<td>99.25 ± 0.04^A</td>
</tr>
<tr>
<td>HeLa</td>
<td>0</td>
<td>100 ± 0.00^a</td>
<td>59.25 ± 4.31^b</td>
<td>40.00 ± 4.10^c</td>
<td>0.00 ± 0.00^d</td>
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</tr>
<tr>
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<td>100 ± 0.00^a</td>
<td>71.00 ± 0.84^bA</td>
<td>57.30 ± 0.70^c</td>
<td>44.00 ± 1.04^E</td>
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<tr>
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<td>600</td>
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<td>72.45 ± 0.21^bA</td>
<td>61.95 ± 0.21^c</td>
<td>65.45 ± 0.21^d</td>
<td>48.00 ± 0.14^A</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>100 ± 0.00^a</td>
<td>87.05 ± 0.49^bA</td>
<td>82.65 ± 0.50^bA</td>
<td>74.60 ± 0.42^C</td>
<td>62.65 ± 0.35^C</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>100 ± 0.00^a</td>
<td>95.95 ± 0.21^a</td>
<td>95.80 ± 0.14^bA</td>
<td>94.90 ± 0.14^C</td>
<td>94.80 ± 0.14^C</td>
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Small letter and capital letter superscripts indicate significant differences (p < 0.05) in the columns and rows, respectively.

DISCUSSION

This work aimed to determine the anticancer properties of L. plantarum KK518, a probiotic bacterium isolated from Pak-Sian Dong in Thailand. L. plantarum is a beneficial microorganism that is extensively used as a starter culture for various Asian fermented food products.11 L. plantarum produces large amounts of organic acid during kimchi fermentation and produces natural antibacterial and antifungal products.11

L. plantarum's chemopreventive potential has been reported. L. plantarum, isolated from kimchi, was able to exhibit a strong antimutagenic effect against N-methyl-N’-nitro-N-nitrosoguanidine, 4-Nitroquinoline-1-oxide.12 Moreover, L. plantarum, isolated from kimchi, had more potent antimutagenic effects compared to LAB originated from fermented milk.13 It has been hypothesized that polysaccharide types on the cell wall of L. plantarum rather than glycopeptide play a pivotal role in cancer suppression.14

To evaluate cytotoxicity of L. plantarum KK518 extract on three different cancer cells including HepG2, HeLa, and MCF-7, MTT colorimetric assay as a routine technique was conducted. This technique relies on the ability of live cancer cells to metabolize the yellow tetrazolium salt MTT to a blue crystalline formazan product while dead cells are unable to do so.15 HeLa cells (IC_{50} of 371.97 µg/mL and 90.88% cytotoxicity at 1,000 µg/mL) were most cytotoxic to L. plantarum KK518 extract over 48 h of exposure whilst MCF-7 cells were least cytotoxic (IC_{50} of 682.53 µg/mL) to the bacterial extract. Likewise, L. plantarum KK518 extract was most antiproliferative towards HeLa cells using anti-colony formation test since the bacterial extracts at 600, 800 and 1,000 µg/mL over 48 h led to a complete inhibition of colony formation; however HepG2 was most resistant
to the bacterial extract (IC₅₀ of 418.52 µg/mL). Similarly, HepG2 cells seemed to be most resistant to antimigratory effects. Overall, *L. plantarum* KK518 extract was likely to be effective in treating cancers in the following order: HeLa > MCF-7 > HepG2.

However, components in the bacterial extract responsible for the observed effects are yet to be identified. The possible molecules that play a key role in the cytotoxicity of extracted bacterial metabolites include active proteins that binds to procarcinogenic compounds or non-protein molecules such as short-chain fatty acids including butyrate and propionate.

Previously, *L. plantarum* 70810 isolated from Chinese Paocai was able to produce exopolysaccharide (EPS) with moderate antitumor activity against HepG2 cells (56.34 % cytotoxicity at 600 µg/mL EPS extract) after a prolonged time (72 h) of treatment. When compared to our finding, *L. plantarum* KK518 extract was less effective in treating HepG2 cells (27.05% cytotoxicity at 600 µg/mL bacterial extract) after 48 h of exposure than *L. plantarum* 70810 EPS. This may be due to the purer form of EPS treatment than our crude bacterial extract treatment and longer time of exposure to HepG2 cells. In accordance with our work, *L. plantarum* 5BL isolated from the vaginal secretion of a healthy and fertile Iranian woman elicited a significant antiproliferative effect on HeLa for all incubation times and doses used. The greatest antiproliferative effect on HeLa was observed at the highest dose (50 µg/mL) of the metabolite and was greater against HeLa cells than against MCF-7 cells.

In contrast to our finding, six bacteriocin-producing *L. plantarum* identified as I-UL4, TL1, RSS, RI11, RG11 and RG14 strains isolated...
from Malaysian foods produced postbiotic metabolites that were more cytotoxic against MCF-7 cells than HeLa and HepG2 cells. In addition, L. plantarum 15HN isolated from traditional dairy products exhibited no significant anticancer effects on MCF-7, and HeLa cells. Moreover, cytotoxicity analysis of plantaricin from L. plantarum DM5 isolated from indigenous fermented beverage Marcha from India on HeLa cell lines revealed its non-toxic nature towards HeLa cells.

Compared to these previous reports, our L. plantarum KK518 extract seemed to be more efficacious towards HeLa and MCF-7 cells than those of L. plantarum 15HN and plantarum DM5.

In the previous study, blueberries fermented with L. plantarum showed higher antioxidant activities and antiproliferative activities against HeLa cells than did raw blueberries. L. plantarum fermentation bifructose blueberry polyphenols into active phenol metabolites with strong antioxidant and antiproliferative activities. For future practical application, L. plantarum KK518 can be used as a starter culture to ferment functional foods with chemopreventive benefits.

CONCLUSION

This work revealed that L. plantarum KK518 extracts may have potential anticarcinogenic activity in HepG2, MCF-7 and HeLa cancer cells through the dual effect of cell proliferation inhibition, induction of apoptosis and cell migration inhibition. Since literature on cytotoxic and antiproliferative activity of L. plantarum is still limited, its mechanisms on cellular levels and gene expressions requires further investigations. Overall, L. plantarum KK518 extract appears to have potential as a bio-therapeutic and can be implemented for functional food product development with chemopreventive benefits.

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CONFICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

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**GRAPHICAL ABSTRACT**

![Graphical Abstract Image]

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