An Iodine Treatments Effect on Cell Proliferation Rates of Breast Cancer Cell Lines; In Vitro Study

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Introduction

Iodine plays a pivotal role in maintaining the mammary gland’s normal healthy integrity and its deficiency transmutes a healthy structure and function of rat mammary gland [1], [2]. Some of the studies reported that iodine mediates apoptosis and has an effect on antineoplastic process [3], [4], [5]. Iodine consumption of 3–6 mg/day has reduced breast hyperplasia, per lobular/ductal fibrosis, and slowing down breast cancer progression [6], [7]. Iodine mediates antiproliferative effects directly or indirectly. Oxidized iodine eliminates the mitochondrial membrane potential (MMP) to mediate apoptosis directly or by forming iodolipids and activation of gamma type peroxisome proliferator-activated receptors γ (PPARγ) that trigger apoptosis [2], [5], [8], [9].

Cancer disease is the second leading cause of death globally; it caused more than ten million death annually [10], [11], [12]. The incidence rate of breast cancer in the United States (US) increased slightly by 0.3% per year, but the mortality rate declined by around 40% from 1989 to 2017 [13]. The Asian region has the lowest breast cancer mortality in the world [5]. Globocan report 2018 said that new breast cancer cases in the US are higher than in Japan (7.5%;11%) [12]. Seaweed is a common dietary component in Japanese and it is a rich source of iodine. Japanese iodine consumption is 25 times higher than in Western countries. It has been associated with the low incidence of breast cancer in Japanese people compared to Western [2]. However, breast cancer number in Japan continues to increase that may be exposed to the western diet and lifestyle [14].

Breast cancer was classified based on histopathology findings. Advanced techniques such as immunohistochemistry define the molecular subtypes based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 positive (ERBB2/HER2+) [15], [16], [17]. Identification of the molecular subtypes of breast cancer is essential for a personalized treatment plan and predict prognosis. Some breast cancer subtypes are resistant to some therapies [15], [17], [18]. Limitation of the benefit of available therapy challenges an emerge of new alternative therapy for breast cancer.

BACKGROUND: Iodine can reduce breast tumor progression by mediates an antiproliferative effect.

AIM: This study aimed to investigate the effect of iodine (I2), Lugol (I3K), and the combination of both on cell proliferation of three different types of breast cancer cell lines.

METHODS: The samples were MCF7, SKBR3, and MDA-MB 213 cell lines. Cell proliferation rate was measured using colorimetric and clonogenic assays.

RESULTS: The cell proliferation rate of MDA-MB 231 cells was reduced significantly by treatment I2, I3K, and combination of both with p = 0.046, p = 0.00, and p = 0.00, respectively. In MCF7 cells, I2 reduced the cell proliferation of 54–94% and I3K reduced the proliferation of 74–94%. The effectiveness of I3K treatments in slowing cell proliferation rate was dose-dependent. In SKBR3 cells, I2 reduced proliferation up to 85% and I3K 4%-94% depending on the dose. Clonogenic assay results showed a discontinue of the cell proliferation by all doses of I2 and I3K treatments in slowing tumor progression.

CONCLUSION: Breast cancer cell lines, representing subtypes of luminal A, HER2+, and triple-negative, show an excellent response to iodine treatments and I3K response shows in a dose-dependent manner. Further studies are needed to investigate the effective in vivo doses.
The total amount of iodine in the human body is around 30–50 mg. Less than 30% presents in the thyroid gland. Around 60–80% is concentrated in extrathyroidal tissues. These include salivary glands, gastric mucosa, lactating mammary gland, the choroid plexus, and etcetera [1], [19]. Non-lactating breast tissue is known to be NIS and peroxidase poor and does not provide for organification [4].

$I_2$ is taken up by a non-lactating mammary gland without the involvement of NIS and peroxidase activity, and it is a highly reactive species [2], [4], [20]. $I_2$ mediates antiproliferative effect with direct or indirect action. In vitro studies showed that $I_2$ exposure induced the mitochondria to release apoptosis factors that cause nuclear fragmentation directly [4], [21]. On the other hand, breast tumor tissues contain arachidonic acid (AA) more than the normal ones. Iodination of AA formed 6-iodolactone (6-IL), which is an essential membrane lipid. PPARγ could be the mediator of the 6-IL apoptotic effect [1], [3], [5].

This study investigates the proliferation rates of $I_2$, $I_3K$, or a combination of both in various concentrations treatments of three types of breast cancer cell lines. It will obtain the potential extrathyroidal benefits of iodine and alternative breast cancer therapy.

**Materials and Methods**

**Cell lines and culturing**

This study uses three types of breast cancer cell lines MCF7 (estrogen and progesterone positive receptors/ER+ and PR+) and SKBR3 (human epidermal growth factor receptor 2+/HER2+) and MDA-MB 231 (triple-negative) [18]. SKBR3 was purchased from the American Type Culture Collection, MCF7, and MDA-MB 231 cell lines were gifted from the Faculty of Medicine, Universitas Padjadjaran, Bandung-Indonesia. MCF7 and MDA-MB 231 cells were cultured in RPMI 1640 (Invitrogen). Mediums were added with 10% fetal bovine serum (Invitrogen), 1% penicillin, 1% streptomycin, and 1% amphotericin B. The cells were then grown for 12 days in the mediums. They were supplemented with 10% fetal bovine serum (Invitrogen), 1% penicillin, 1% streptomycin, and 1% amphotericin B. The cells were then washed with PBS, fixed with methanol/water (1:1), and then stained with crystal violet. Macroscopic colonies were counted. These experiments were performed twice. The proliferation rate was calculated as the number of cell colonies in plates treated with $I_2$, $I_3K$, and a combination of both compared with those untreated cells.

**Statistical analysis**

All experiments were performed in triplicate. Results are presented as means ± standard deviation. Statistical significance comparing experimental values used non-parametric tests (Kruskal–Wallis and Mann–Whitney test). One-way ANOVA and post-hoc-Bonferroni for the parametric test were performed.

**Results**

**MDA-MB 231 cell lines**

The averages of the cell proliferation after treatments of $I_2$, $I_3K$, and combination of $I_2$–$I_3K$ (1 µM) were 98 ± 5%, 88 ± 33%, and 110 ± 3%, respectively, 95 ± 6%, 80 ± 6%, and 79 ± 7% respectively, and 55 ± 8%, 53 ± 8%, and 47 ± 7%, respectively, as shown in Table 1. The cell
proliferation rate of MDA-MB 231 cells was reduced significantly by treatment $I_2$, $I_3K$, and combination of both with $p = 0.040$, $p = 0.001$, and $p = 0.001$, respectively, as shown in Figure 1. Treatment doses of 10 µM and 20 µM reduced cell proliferation significantly compared to the dose of 1 µM with $p = 0.001$ and $p = 0.001$.

The antiproliferation rate of $I_2$, $I_3K$, and combination of both for 24, 48, and 72 h treatment, not differ significantly. The treatment combination did not show different results compared to $I_2$, $I_3K$ alone $p = 0.177$, $p = 0.066$, and $p = 0.329$.

### MCF7 cell lines

The averages of the cell proliferation after treatments of $I_2$, $I_3K$, and combination of $I_2$, and $I_3K$ (1 mM) for 24 h were 60 ± 7%, 140 ± 56%, and 273 ± 106%, respectively, for 48 h were 66 ± 31%, 114 ± 98%, and 103 ± 13%, respectively, and for 72 h were 27 ± 17%, 162 ± 22%, and 105 ± 11%, respectively, as shown in Table 2. Iodine treatment showed a reduced cell proliferation rate of MCF7, and the effect did not make a significant difference between those doses, as shown in Figure 2. Treatment of Lugol 10 µM and 20 µM reduced cell proliferation significantly compared to Lugol 1 µM, with $p = 0.001$ and $p = 0.001$, respectively. The combination of $I_2$ and $I_3K$ 10 µM and 20 µM reduced cell proliferation significantly compare to 1 µM dose, with $p = 0.001$ and $p = 0.010$, respectively. There is no significantly different effect on cell proliferation between combination treatments of $I_2$ and $I_3K$ of 10 µM with 20 µM.

### SKBR3 cell lines

The averages of the cell proliferation after treatments of $I_2$, $I_3K$, and combination of $I_2$, and $I_3K$ (1 µM) for 24 h were 29 ± 10%, 96 ± 20%, and 93 ± 23%, respectively, for 48 h were 25 ± 21%, 141 ± 75%, and 111 ± 70%, respectively, and for 72 h were 27 ± 17%, 335 ± 216%, 242 ± 80%, respectively, as shown in Table 3. Iodine reduced proliferation cell up to 85%.

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**Table 1**: MDA-MB231 cells proliferation rate after 1, 10, and 20 µM of $I_2$, $I_3K$, and a $I_2$-$I_3K$ combination

| MDA-MB 231 (%) | Cell proliferation 24 h | Cell proliferation 48 h | Cell proliferation 72 h | p  |
|----------------|-------------------------|-------------------------|-------------------------|----|
| $I_2$          | 98 ± 9                  | 55 ± 8                  | 0.001                   |
| 10             | 95 ± 6                  | 8 ± 8                   | 0.590                   |
| 20             | 10 ± 10                 | 10 ± 10                 | 0.940                   |
| p              | 0.061                   | 0.055                   | 0.063                   |
| $I_3K$         | 88 ± 33                 | 53 ± 8                  | 0.170                   |
| 10             | 80 ± 6                  | 7 ± 7                   | 0.360                   |
| 20             | 16 ± 14                 | 9 ± 7                   | 0.730                   |
| p              | 0.079                   | 0.061                   | 0.055                   |
| $I_2$ + $I_3K$ | 110 ± 3                 | 47 ± 7                  | 0.490                   |
| 10             | 79 ± 7                  | 13 ± 13                 | 0.449                   |
| 20             | 11 ± 18                 | 13 ± 16                 | 0.709                   |
| p              | 0.066                   | 0.055                   | 0.066                   |

**Table 2**: MCF7 cells line proliferation rate after 1, 10, and 20 µM of $I_2$, $I_3K$, and a $I_2$-$I_3K$ combination

| MCF7 (%) | Cell proliferation 24 h | Cell proliferation 48 h | Cell proliferation 72 h | p  |
|----------|-------------------------|-------------------------|-------------------------|----|
| $I_2$    | 60 ± 7                  | 66 ± 31                 | 27 ± 17                 | 0.144 |
| 10       | 52 ± 6                  | 16 ± 11                 | 17 ± 9                  | 0.010 |
| 20       | 28 ± 21                 | 25 ± 19                 | 6 ± 4                   | 0.280 |
| p        | 0.113                   | 0.099                   | 0.177                   |     |
| $I_3K$   | 140 ± 56                | 114 ± 98                | 162 ± 22                | 0.689 |
| 10       | 120 ± 34                | 30 ± 16                 | 26 ± 10                 | 0.001 |
| 20       | 36 ± 24                 | 6 ± 6                   | 12 ± 10                 | 0.154 |
| p        | 0.055                   | 0.042                   | 0.001                   |     |
| $I_2$ + $I_3K$ | 273 ± 106             | 103 ± 13                | 105 ± 11                | 0.021 |
| 10       | 115 ± 28                | 33 ± 9                  | 21 ± 9                  | 0.065 |
| 20       | 32 ± 22                 | 14 ± 6                  | 14 ± 11                 | 0.275 |
| p        | 0.010                   | 0.000                   | 0.000                   |     |
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Clonogenic result

Iodine treatment in varying doses discontinues the cell proliferation, as shown in Table 4 and Figure 4. Even though I,K (1 µM) dose did not affect in the slowing of cell proliferation, but 10 µM and 20 µM doses suppressed cell proliferation.

Table 3: SKBR3 cells proliferation rate after 1, 10, and 20 µM of I, I,K and combination of I,I,K treatments

Table 4: The clonogenic assay results in MDA-MB 231, SKBR3, and MCF7 cell lines after 1 µM, 10 µM, and 20 µM of I, I,K treatments

Discussion

In thyroid cell and lactating mammary gland, iodide transport is facilitated by NIS [6], [22]. Iodide excess induces apoptosis in thyrocytes, and the effect depends on thyroid peroxidase [3]. On the other hand, non-lactating mammary gland has a low level of peroxidase. The condition does not provide the environment for iodide organification. However, I can be utilized without sodium iodide symporter and peroxidase [19], [23]. I2 treatment in benign breast cancer has been found to reduce tumor size and symptoms, but not I- treatment [6]. Iodide is preferentially taken up and retained in the thyroid and lactating mammary glands, but the pituitary, ovary, and non-lactating breast glands, I2 are taken up more readily than I- [6], [22].

Iodine in breast tissue was explained by in vitro studies that I2 is taken up through diffusion, then incorporated into iodolipids and nuclear components, then exert antiproliferative and apoptotic properties [3], [19], [24]. Previous studies have reported that the antiproliferative effects of I2 are through MMP destruction that directly results in apoptosis. MMP is needed for mitochondrial functions such as ATP production, metabolite transport regulation, and protein import. The mitochondrial intermembrane space contains several proteins that induce apoptosis through cytochrome c induction or activation of a caspase-independent apoptotic death program [3], [8], [9], [25]. Furthermore, iodine’s antiproliferative effect can occur through iodolipid formation, 6-IL, or alpha-iodohexane canal, and the activation of PPARγ interaction through increased BAX, caspases 3, 7, p53, and p21 [1], [3], [21], [25].
Recently, a study has reported that I\textsubscript{2} treatment did not have an antiproliferative effect in MDA-MB 231 cells [4]. This study found that the proliferation MDA-MB 231 cell discontinued by I\textsubscript{2} treatment, as shown in Figures 1 and 4. The low dose of I\textsubscript{2}K (1 \(\mu\)M) showed a limitation of the MDA-MB 231 cells' antiproliferation effect. However, 10 \(\mu\)M and 20 \(\mu\)M of I\textsubscript{2}K and a combination of I\textsubscript{2} and I\textsubscript{2}K reduced cell proliferation significantly with \(p < 0.05\) (Table 1). A combination of treatments did not show an increasing effect when it is compared with I\textsubscript{2} and I\textsubscript{2}K alone. I\textsubscript{2}K reduces cell proliferation effect in this study, in line with a study by Rösner et al. [6]. The clonogenic result showed that I\textsubscript{2} doses inhibited cell proliferation and I\textsubscript{2}K (10 \(\mu\)M and 20 \(\mu\)M), as shown in Figure 4. However, the mechanism of iodine induces apoptosis in MDA-MB 231 has yet to be elucidated.

Meanwhile, I\textsubscript{2} inhibited the proliferation of MCF7 cells was not a dose-dependent manner (Table 2). The treatment reduced cell proliferation by up to 94%. This finding has a similar result with previous studies [3], [5], [26]. Furthermore, a study...
reported that I\(_\text{2}\) treatment was found to inhibit MCF7 cell growth, that even more effective than in MDA-MB 231 cells [1], [21]. In this study, I\(_\text{2}\) treatments show similar effective in MCF7, MDA-MB 231, and SKBR3 cells from the clonogenic result. I\(_\text{2}\) treatment increases the apoptotic rate and PPAR\(\gamma\) expression, leading to a decrease in proliferation and dissipating the estrogen receptor alpha’s translocation to the nucleus [3]. As MCF7 and MDA-MB 231 cells express PPAR\(\gamma\) receptors, it can be hypothesized that the antiproliferation mechanism of I\(_\text{2}\) in both cell lines is likely to be through iodine-PPAR\(\gamma\) receptor interactions [21], [27]. Further studies are needed to explore it. Furthermore, I\(_\text{2}\)K treatments showed an antiproliferation effect on MCF7 exerts a dose-dependent manner. Nevertheless, a combination of I\(_\text{2}\) and I\(_\text{2}\)K inhibited cell proliferation did not increase significantly compared with I\(_\text{2}\)K treatment alone, as shown in Table 2. The clonogenic result showed that I\(_\text{2}\)K (10 \(\mu\)M and 20 \(\mu\)M) effectively to stop cell proliferation (Figure 4).

SKBR3 cells do express NIS and showed that they could take radioiodine [28], [29]. In this study, I\(_\text{2}\) and I\(_\text{2}\)K showed an antiproliferative effect, as shown in Table 3. The iodine effect did not change by a different dose. However, antiproliferative effect of I\(_\text{2}\)K and the combination of I\(_\text{2}\) and I\(_\text{2}\)K tend to increase with higher doses (Table 3). The clonogenic result showed I\(_\text{2}\)K (10 \(\mu\)M and 20 \(\mu\)M) effectively to discontinued SKBR3 cell proliferation (Table 4). Further investigations are needed to elaborate on the mechanism of the apoptotic process of iodine exposure in breast cancer.

Conclusion

Iodine treatment was sufficient to discontinue cell proliferation of MCF7, MDA-MB231, and SKBR3 cells. The antiproliferative effect of I\(_\text{2}\)K shows in a dose-dependent manner. Breast cancer cell lines, representing subtypes of luminal A, HER2+, and triple-negative, show an excellent response to iodine treatments. Further studies are needed to investigate the effective dose of iodine to breast cancer subtypes in vivo and the effect toward the normal cell. This finding opens the opportunity of using iodine for breast cancer prevention as well as an alternative therapy.

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Ethical clearance

The subject in this research was cell lines; the authors did not have any contact with human or animal subjects, hence, not applicable.

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