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Cytotoxic Activity of Mangosteen (*Garcinia mangostana* L.) Peel Extract and α-Mangostin toward Leukemia Cell Lines (HL-60 and K-562)

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Abstract

Fruit of Mangosteen (*Garcinia mangostana* L.) is well-known in Indonesia and other Southeast Asian countries. Studies have shown that extracts of the pericarp of mangosteen contained mostly of xanthones exhibit many biological activities, especially as an antitumor. This study aimed to investigate the cytotoxic activity and selectivity of Mangosteen Peel Extract (MPE) and α-mangostin against two leukemia cell lines (HL-60 and K-562) and the normal lymphocyte cells from two different donors. The cytotoxic activity was performed using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. Imatinib and Isotretinoin were used as a positive control to the K-562 and HL-60 cells, respectively. The MPE and α-mangostin revealed higher mortality toward leukemia cell lines rather than toward lymphocyte cells, with more than 80% of HL-60 and K-562 cells died at 6.25 and 25 µg/ml, respectively. MPE was more toxic and selective against K-562 with IC50 of 2.79 µg/ml and SI of 8.27, while α-mangostin was more toxic and selective against HL-60 with IC50 of 1.12 µg/ml and SI of 22.34. MPE and α-mangostin showed potent sensitivity and selectivity to leukemia cells, therefore is a promising source for future leukemia treatment.

Keywords: Mangosteen Peel Extract, α-mangostin, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), selectivity index

1. Introduction

Cancer has been the second cause of death after cardiovascular diseases in the world. There were around 8.2 million of people died because of cancer and about 14.1 million of new cancer cases were detected in 2012. Particularly in Indonesia, there was about 0.1% of total people suffering from cancer with 74.6% of mortality rate in male and 63.3% in female. Lung or bronchus cancer, prostate cancer in men, breast cancer in the female, and colon or rectum cancer reveal as the most deadly cancer worldwide. However, rare cancer such as leukemia is also a cause of death because of its destructive nature. According to the GLOBACAN, the percentage of leukemia was 2.5% of total new cases, contributing to 3.2% of total deaths by cancer in 2012 which was mostly suffered by children.

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Characterized by high numbers of abnormal white blood cells, leukemia has been grouped into lymphoblastic and myeloid leukemia, namely Chronic Lymphocytic Leukemia (CLL) or Acute Lymphocytic Leukemia (ALL) and Chronic Myelogenous Leukemia (CML) or acute Myelogenous Leukemia (AML). Leukemia can be treated using interferon-α (IFN-α), Stem Cell Transplantation (SCT), radiotherapy and chemotherapy. Imatinib, a chemotherapy agent of tyrosine-kinase inhibitor, has been used as the first-line treatment for CML. It induces apoptosis and inhibition of proliferation by inhibiting the phosphorylation and binding process of Bcr-Abl oncoprotein. Another chemotherapy agent for leukemia is retinoic acid, vitamin A derivative such as All-Trans Retinoic Acid (ATRA) and isotretinoin. They are used for several cancer treatment and remission including for Acute Promyelocytic Leukemia (APL), a subtype of AML by inducing cell apoptosis. However, the usage of imatinib and retinoic acid as well as the other chemotherapy agents can generate side effects by damaging the normal cells and lead to the development of the multidrug resistance cancer. Therefore, the finding of the safe, selective, and sensitive chemicals that have anticancer property is still needed.

Mangosteen (Garcinia mangostana L.) has been used as a traditional medicine to treat diseases related to immune and gastrointestinal for decades. Its extract contains several active compounds, including terpenes, anthocyanins, tannins, phenols, and xanthones. Xanthones have been shown to have several pharmacological properties, including as an antitumor. The most abundant and the most studied xanthones are α-mangostin, β-mangostin, γ-mangostin, garcinone E, and gartanin, and those xanthones possess great biological activities such as anti-allergy, anti-inflammatory, antioxidant, anti-tumor, antibacterial, antifungal and antiviral activities, neuroprotective, cardioprotective, and immunomodulation. Prior studies revealed that α-mangostin were the most abundance xanthone derivative from the aqueous, acetone and methanol extract of mangosteen. Therefore, this study aimed to investigate the cytotoxic activity and selectivity of Mangosteen Peel Extract (MPE) and α-mangostin against two leukemia cell lines (HL-60 and K-562) and the normal lymphocyte cell lines from two different donors. The 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium MTS assay was used to investigate the cytotoxic effect of the MPE, α-mangostin, imatinib, and isotretinoin. Those data are used to reveal the IC$_{50}$ and Selectivity Index (SI) of the MPE and three other compounds to the H-60 and K-562 cell lines. The in vitro result demonstrates that MPE and α-mangostin have a potential to use against leukemia by showing the higher cytotoxic effect and selective index to leukemia rather than the imatinib and isotretinoin.

2. Materials and Methods

2.1 Mangosteen Peel Extract (MPE) Preparation

The peels of Garcinia mangostana L. from Cisalak-Subang, West Java, Indonesia were determined by the herbarium staff of Biology Department, School of Life Sciences and Technology, Bandung Institute of Technology, Bandung, West Java, Indonesia. Around 350 g of chopped and dried-mangosteen peels were extracted using steady-state extraction (maceration) method. The chopped and dried peels were immersed in ethanol 70% for 24 hours and filtrated. The filtration was repeated until the filtrate became colorless. The filtrate was evaporated with a rotary evaporator at 40°C and the ethanolic extract of mangosteen peel was collected and stored in a freezer with the temperature of -20°C.

2.2 Leukemia Cell Lines Cultivation

Two different leukemia cell lines, human acute promyelocytic (HL-60) and human chronic myelogenous (K-562) were obtained from Stem Cells and Cancer Institute (SCI) Jakarta, Indonesia. Cell lines were cultured in supplemented Iscove’s Modified Dulbecco’s Medium (IMDM) (Biowest, France), 2% Penicillin-Streptomycin (Biowest, France), 10% Fetal Bovine Serum (FBS) (Biowest, France) and were incubated at 37°C in a humidified incubator with 5% CO$_2$. After 24 hours of incubation, the number of viable cells was counted using a haemocytometer with tryphan blue staining to obtain a sufficient cell number for the cytotoxic assay.

2.3 Lymphocyte Isolation and Cultivation

Lymphocyte isolation from two healthy donors was approved by Ethnic Commission Number 232/KEP/I/2016 of Maranatha Christian University-Immanuel Hospital Bandung, Indonesia. The healthy donors have signed the informed consent. After taken from donors, to separate the lymphocyte from other leukocytes histopaque (Sigma-
Aldrich, U.S.A.) was added into the whole blood. Whole blood then was centrifuged at 1,800 rpm for 5 minutes to obtain the blood buffy coat. The blood buffy coat was added with 1x Phosphate Buffer Saline (PBS) (Biowest, France) and was centrifuged at 1,800 rpm for 10 minutes in 4°C. Then, the pellet was added with 1x PBS and was centrifuged at 1,500 rpm for 10 minutes in 4°C. The final pellet contained leukocytes was maintained in Rosewell Park Memorial Institute Medium (RPMI) (Biowest, France) and supplemented with 1% non-essential amino acids, 1% 1-glutamine, 100 U/ml penicillin, 10mg/mL streptomycin and 10% heat-inactivated fetal calf serum (Biowest, France) then incubated at 37°C in humidified air containing 5% CO₂.

2.4 Cytotoxic Assay

Approximately 100 μL of lymphocyte, HL-60 and K-562 cell suspension contained 10⁵ cells/ml were seeded in each well of 96-well plate. Following that, 100 μL of Isotretinoin (Roche, Switzerland) in different levels (100, 85, 70, 55, 40, and 25 μM) were added into the wells of lymphocyte and HL-60. Imatinib (Glivec, Novartis) in different levels (100, 50, 25, 12.5, 6.25, and 3.125 μM) were added into the wells of lymphocyte and K-562. α-mangostin (Cengdu Biopurify Phytochemical, China) (100, 50, 25, 12.5, 6.25, and 3.125 μM) and Mangosteen Peel Extract (MPE) (100, 50, 25, 12.5, 6.25, and 3.125 μg/mL) were added into the wells of lymphocytes, HL-60, and K-562. Cells then incubated at 37°C with 5% CO₂ for 24 hours. Then, 20 μL of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxyme-thoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) (Promega, U.S.A.) was added into each well and plate was incubated at 5% CO₂, 37ºC for 3 hours. Finally, the absorbance used to calculate the percentage of cell mortality (Equation 1) was measured at 490 nm with Multiskan GO (Thermo Scientific, U.S.A). Wells of each cell that not supplemented with the compounds presented as the negative control.

\[
\text{Cell Mortality} \% = \left( \frac{A_{\text{untreated cell}} - A_{\text{treated cell}}} {A_{\text{untreated cell}}} \right) \times 100 \%
\]

\[A_{\text{treated cell}}: \text{Absorbance of cells treated with either MPEE, } \alpha\text{-mangostin, imatinib, or isotretinoin;}
\]

\[A_{\text{untreated cell}}: \text{Absorbance of untreated cells}
\]

2.5 Selectivity Analysis

The Selectivity Index (SI) describes the selectivity of the MPE, α-mangostin, imatinib, and isotretinoin toward the leukemic cell lines. The index was calculated from IC₅₀ ratio of the lymphocytes and the cancerous cell line (HL-60 or K-562) (Equation 2)¹⁵. The compound with SI higher than 3 revealed a high selective compound against the HL-60 or K-562, and the opposite was a less selective compound.

\[
\text{Selectivity Index (SI) } = \frac{\text{IC}₅₀ \text{ of normal cell}}{\text{IC}₅₀ \text{ of cancer cell}}
\]

IC₅₀ of normal cell: The value of median inhibitory concentration (IC₅₀) of lymphocyte cells;

IC₅₀ of cancer cell: The value of median inhibitory concentration (IC₅₀) of cancer cells

2.6 Statistical Analysis

All treatment in this study did independently and conducted in triplicate. SPSS Statistic 17.0 for Windows was used to calculate the IC₅₀ of the compounds and the significant differences using probit analysis and one-way ANOVA, respectively. The mortality and viability data were presented as mean ± Standard Deviation (SD).

3. Results

3.1 Cytotoxic Effect of Each Compound toward HL-60, K-562, and Leukocyte

Table 1 to 4 are showing the cytotoxic effect of imatinib, isotretinoin, α-mangosteen and MPE presented as the percentage mortality of HL-60, K-562, and leukocyte. Isotretinoin and α-mangostin started at the concentration of 25 μM had more than 50% mortality to HL-60 and K-562, respectively. Imatinib and α-mangostin started at 12.5 μM showed more than 50% mortality to K-562 and HL-60, respectively (Table 1-3). Those of MPE started at 3.125 μg/ml and at 6.25 μg/ml revealed more than 50% mortality to HL-60 and K-562, respectively (Table 4). Furthermore, Figure 1 shows HL-60 and K-562 cell lines have lower density in a higher concentration of MPE and α-mangostin treatments.
Cytotoxic Activity of Mangosteen (*Garcinia mangostana* L.) Peel Extract and α-Mangostin toward Leukemia Cell Lines (HL-60 and K-562)

**Table 1**: The percentage mortality (%) of Lymphocyte and K-562 treated with Imatinib in six different concentrations

| Cells   | Concentration (µM)  | 100      | 50       | 25       | 12.5     | 6.25     | 3.125    |
|---------|---------------------|----------|----------|----------|----------|----------|----------|
| Lymphocyte | 74.67 ± 11.09b | 10.71 ± 5.82a | 6.09 ± 6.48a | 5.67 ± 6.57a | -5.81 ± 1.92a | -22.88 ± 10.86a |
| K-562   | 94.64 ± 0.11f | 76.89 ± 1.01c | 63.43 ± 0.74a | 55.95 ± 0.99c | 51.95 ± 0.9b | 47.5 ± 0.8a |

Data presented as mean ± standard deviation, different superscript letters in each row (Lymphocyte, K-562) showed a significant difference at p<0.05 (Tukey HSD post hoc test) among the concentrations.

**Table 2**: The percentage mortality (%) of Lymphocyte and HL-60 treated with Isotretinoin in six different concentrations

| Cells   | Concentration (µM)  | 100      | 85       | 70       | 55       | 40       | 25       |
|---------|---------------------|----------|----------|----------|----------|----------|----------|
| Lymphocyte | 91.74±12.07b | 60.39±17.70b | 54.93±34.16b | 39.4±14.56b | 15.05±4.31b | -38.14±11.43a |
| HL-60   | 99.05±1.11f  | 95.41±2.19de | 83.48±1.02cd | 80.53±2.48bc | 69.52±4.66b | 51.73±2.86a |

Data presented as mean ± standard deviation, different superscript letters in each row (Lymphocyte, HL-60) showed a significant difference at p<0.05 (Tukey HSD post hoc test) among the concentrations.

**Table 3**: The percentage mortality (%) of Lymphocyte, HL-60, and K-562 treated with α-Mangosteen in six different concentrations

| Cells   | Concentration (µg/ml) | 100      | 50       | 25       | 12.5     | 6.25     | 3.125    |
|---------|-----------------------|----------|----------|----------|----------|----------|----------|
| Lymphocyte | 67.53±25.83aA | 49.9±1.88aA | 33.8±26.82aA | 29.32±7.07aA | 22.6±37.28aA | 19.38±1.11aB |
| HL-60   | 95.72±0.43dA | 94.55±0.07dB | 94.51±0.65dB | 75.1±0.27B | -29.44±0.5dB | -45.36±7.4aA |
| K-562   | 96.2±0.11dB | 94.65±0.3dB | 91.29±0.27dA | 16.31±0.65cA | -21.72±3.08bA | -68.47±8.35aA |

Data presented as mean ± standard deviation, different lowercase of superscript letters in each row (Lymphocyte, K-562, HL-60) showed a significant difference at p<0.05 (Tukey HSD post hoc test) among the concentrations, different uppercase of superscript letters in each column (100, 50, 25, 12.5, 6.25, 3.125) showed a significant difference at p<0.05 (Tukey HSD post hoc test) among the cells.

**Table 4**: The percentage mortality (%) of Lymphocyte, HL-60, and K-562 treated with MPE in six different concentrations

| Cells   | Concentration (µg/ml) | 100      | 50       | 25       | 12.5     | 6.25     | 3.125    |
|---------|-----------------------|----------|----------|----------|----------|----------|----------|
| Lymphocyte | 94.96±12.46eA | 55.91±8.82bA | 44.86±1.13abA | 42.2±1.46bA | 37.3±5.4abA | 16.17±3.71A |
| HL-60   | 106.7±1.85bcA | 100.97±0.67bb | 106.8±0.52bcC | 109.1±1.7bC | 101.65±1.36bcC | 89.7±1.11bC |
| K-562   | 98.08±0.83dA | 95.06±2.95cdB | 93.14±4.21cdB | 86.24±0.76bcB | 73.16±0.23bB | 46.23±0.65aB |
3.2 Sensitivity and Selectivity of Each Compound toward HL-60, K-562, and Leukocyte

Further analysis of percentage mortality of the compounds using probit regression revealed that the IC₅₀ of imatinib, isotretinoin, MPE, and α-mangostin were high to normal lymphocyte and the IC₅₀ MPE and α-mangostin were comparably low to the leukemia cell lines (Figure 2). MPE possessed the lowest IC₅₀ (2.79 µg/ml) toward K-562 whereas α-mangostin possessed the lowest IC₅₀ (1.12 µg/ml) to HL-60 (Table 5). The result of selectivity index showed that isotretinoin, a recent chemotherapy agent used to treat leukemia was less selective than MPE and α-mangostin toward HL-60, whilst imatinib was more selective toward K-562 than MPE and α-mangostin. Nevertheless, MPE and α-mangostin showed high selectivity toward both of HL-60 and K-562, with selectivity index was more than 3 (Table 5).

Table 5: The cytotoxicity and selectivity of MPE, α-mangostin, imatinib and isotretinoin against HL-60, K-562, and leukocyte

| Compounds       | HL-60 IC₅₀ (µg/ml) | K-562 IC₅₀ (µg/ml) | Lymphocyte IC₅₀ (µg/ml) |
|-----------------|--------------------|--------------------|-------------------------|
| MPE             | 1.16               | 2.79               | 23.08                   |
| α-mangostin     | 1.12               | 7.21               | 25.02                   |
| Isotretinoin    | 7.66               | -                  | 21.93                   |
| Imatinib        | -                  | 2.84               | 34.35                   |

a. Selectivity Index, calculated based on the ratio of IC₅₀ lymphocyte and the respective leukemic cell line. 
b. Mangosteen peel extract.
Cytotoxic Activity of Mangosteen (Garcinia mangostana L.) Peel Extract and α-Mangostin toward Leukemia Cell Lines (HL-60 and K-562)

Fig. 2. IC\textsubscript{50} values of isotretinoin, imatinib, Mangosteen Peel Extract (MPE) and α-mangostin toward leukemia cell lines (HL-60 and K-562) and normal lymphocyte.

4. Discussion

The activities of xanthones and its derivates to inhibit certain molecular target in cancer progression are related to the tricyclic scaffold and its position\textsuperscript{8}. As an anti-cancer, xanthones arrest cell cycle, induce apoptosis, and differentiation but inhibit the tumor cell proliferation, adhesion, invasion, and metastasis\textsuperscript{16–18}. Xanthones were also reported to prevent initiation stage of cancer by inducing Quinine Reductase (QR) and inhibiting cytochrome P450 (CYP) activity\textsuperscript{9,19}.

In this study, imatinib, isotretinoin, MPE, and α-mangostin showed a cytotoxic effect on the HL-60, K-562, and lymphocyte cells in a concentration-dependent manner. Microscopic images showed the cell density gradually decreased in the higher concentration of each treatment (Figure 1). This result was supported by the percentage of mortality data that showed the cell mortality increased in higher concentration of each treatment. Based on the Table 5, the IC\textsubscript{50} value of MPE and α-mangostin toward HL-60 and K-562 cell lines was lower than the IC\textsubscript{50} value toward lymphocyte, with the selectivity index higher than 3. These findings suggested that MPE and α-mangosteen were safe against the normal lymphocyte, and possessed a high selectivity and sensitivity toward HL-60 and K-562 [8, 15]. These results were consistent with Matsumoto et al.\textsuperscript{22} study.
that showed the antiproliferative activity of xanthones in mangosteen pericarp against human leukemia. The α-mangostin mediates mitochondrial apoptotic pathway in human promyelocytic leukemia (HL-60) by activating the caspase-3 and caspase-9. Together with β-mangostin, γ-mangostin, and methoxy-β-mangostin, these compounds arrest the cell cycle via expression of cyclin proteins in the human colon cancer cells (DLD-1). Furthermore, other anti-tumor activities of mangostins in several cancers have also been reported, including the inhibition of TCF/β-catenin transcription in colon cancer cells and inhibition of cell growth signaling pathways in chondrosarcoma. These findings suggest that xanthones work by various pathways to cancer cells.

In contrast, isotretinoin was either less selective or less sensitive toward the HL-60 cells compared with MPE and α-mangostin. Cancer has been known to be able to develop resistance towards chemotherapy. The resistance of leukemic cell lines to retinoic acid derivate might occur in molecular level by affecting several proteins functions; the mutations of the RARα receptor in APL can block the initiation of differentiation by retinoic acid. On the contrary, Imatinib show good sensitivity and selectivity toward K-562 human Chronic Myeloid Leukemia (CML) cells. Chronic myeloid leukemia is characterized by the presence of a Bcr-Abl fusion gene, which is caused by a reciprocal translocation of chromosomes 9 and 22. The cytotoxic activity of imatinib was supported by other study, demonstrated that imatinib was able to inhibited Bcr-Abl kinase activity led to inactivation of survival pathways and induced long-term activation of caspases that responsible for the degradation and inactivation of Bcr-Abl tyrosine kinase as well as apoptosis of the K562 cells.

## 5. Conclusion

Taken together, our data suggest that MPE and α-mangostin possessed potent sensitivity and selectivity against leukemia. Both of them revealed higher selectivity and sensitivity than isotretinoin toward HL-60 cell line, while MPE also show high sensitivity and selectivity toward K-562 cell line, showing its great potential for pharmaceutical application. We suggest that MPE can be produced as a safe, efficient and low cost of an alternative remedy to fight leukemia. Therefore, the further study of mangosteen peel extract in molecular and in vivo study must be conducted.

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