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Anti-Cancer Activity of The Combination of Marine Mineral Consentrates and α Mangostin on Prostate Cancer Line DU 145 and HEK 293 By WST-8 Method

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Abstract: Marine mineral concentrates have good activity against normal cells, but are less effective against cancer cells. This research was carried out by combining concentrations of sea minerals with natural ingredients that have anti-cancer potential, one of which is α-mangostin. This study aims to determine the IC50 of the combination of α-mangostin, marine mineral concentrate, the combination of α-mangostin & marine mineral concentrate when compared cisplatin and evaluate the activity of α-mangostin, KML and the combination of α-mangostin and KML compared with ciplatin against the DU 145 cancer cell line and HEK 293. The method used is cytotoxicity testing using the WST-8 method. The results of the test materials were α-Mangostin 16.89 ppm, the combination of α-Mangostin-KML with a concentration of 12.5 ppm, namely 1,732 ppm, the combination of α-Mangostin-KML with a concentration of 25 ppm, namely 4,930 ppm, the combination of α-Mangostin-KML with concentration of 50 ppm 5,194 ppm, and cisplatin 4,649 ppm. The results of data analysis show significant differences for all samples. Conclusion α-Mangostin helps KML increase the cytotoxic effect on DU 145 cancer cells and sea mineral concentrate helps reduce the cytotoxic effect of α-Mangostin on normal HEK-293 cells.

Keywords: α-mangostin; Cisplatin; Marine Mineral Concentrate; Prostate cancer

Introduction

Prostate cancer is a medical condition characterized by the growth of cells that grow abnormally, which is caused by uncontrolled growth and development of prostate gland cells, the most common form of prostate cancer is *adenocarcinoma* prostate (Pamungkas, 2021). According to Globocan (The Global Cancer Observatory) in 2020, prostate cancer is the most common type of cancer in men, with an incidence in Indonesia of 13,563 sufferers with a death toll of 4,863 (Globocan, 2020).

Efforts to treat cancer continue to develop, but the treatment also depends on the status and level of the disease, and the age of the sufferer (Doyan et al., 2021). The treatment carried out varies, starting from radical prostatectomy, radiotherapy, hormonal therapy, and chemotherapy (Sanjaya et al., 2024). Chemotherapy using conventional drugs still has many limitations, including relatively fast drug metabolism before it reaches the tumor site, and side effects on normal tissue (Nurmawanti et al., 2023). Surgery also does not provide suitable results because prostate cancer cases often have metastasized (Kamijima et al., 2022). Therefore, technological innovation is needed in prostate cancer therapy which can increase the effectiveness of

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treatment with low toxicity, namely by using natural ingredients (Hama & Tate, 2023).

There are several studies that have been conducted regarding the potential of minerals as anticancer agents, one of these minerals is magnesium (Dominguez et al., 2021). Magnesium is contained in many marine minerals (Giman & Mahmiah, 2019). Preliminary tests, it was seen that marine mineral concentrate had good activity against normal cells, but was less effective against cancer cells (Sudirman & Zain, 2023). The research carried out a combination of sea mineral concentrations with natural ingredients that have the potential to act as anticancer agents, one of which is α-mangostin (Kristiani et al., 2024).

α-Mangostin is a natural xanthone which is mainly produced from the rind of the mangosteen fruit (*Garcinia mangostana*) which is usually known as mangosteen, xanthones are compounds that have a tricyclic aromatic ring structure which undergoes substitution with various phenolic, methoxy and isoprene groups which have a wide spectrum of pharmacological properties, for example anti-inflammatory, antibacterial, antifungal and antioxidant (Karlina et al., 2023). In addition, α-mangostin has recently received a lot of attention because of its efficacy in various types of cancer, including lung cancer, breast cancer, liver cancer, colon cancer, prostate cancer, cervical cancer, and skin cancer (Sakpakdeejaroen et al., 2022).

Previous research suggests that marine minerals originating from Japan has the effect of inhibiting cell migration and metastasis of breast cancer cell lines MCF7 and MDA-MB-231 through the signaling pathway *transforming growth factor-β* (TGF-β) and Wnt (Kim *et.al*., 2013). And in previous research, xanthones reduced the viability of DLD-colon cancer cells, α-mangostin was the most effective with an IC50 of 7.5 µM. A-mangostin showed normal cellular functions were disrupted and the expression of MAP and AKT kinase as well as pERK changed over time (Nauman & Johnson, 2022).

This study aims to determine the IC50 of the combination of α-mangosteen, marine mineral concentrate, the combination of α-mangostin & marine mineral concentrate when compared with cisplatin and evaluate the activity of α-mangostin, marine mineral concentrate and the combination of α-mangostin and marine mineral concentrate when compared with ciplatin against the DU 145 and HEK 293 cancer cell lines (Pradana et al., 2023).

Method

This research is a laboratory experimental study that tests the anticancer activity of a combination of Sea Mineral Concentrate and α-mangostin on the DU 145 prostate cancer cell line and HEK 293 cells using the WST 8 method.

Tools and Materials

Tools

Measuring cup (Pyrex), chamber, tweezers, ruler, analytical balance (Precisa), dropper pipette, beaker (Pyrex), test tube (Pyrex), Erlenmeyer (Pyrex), microplate reader *with* a 450-490 nm, 96 *well microplate*, multichannel pipette (8 or 12 channels ; 10-100 µl), 6 *well plate* (Nest), 100 mm plate (Nest), serological pipettes 5 ml, 10 ml, 25 ml (Nest), micropipettes (Eppendorf) in various sizes and pipette tips 1000 µl (GenFollower), 200 µl (GenFollower).

Material

The test materials, namely α-mangostin and marine mineral concentrate, are the collection of the Pharmacy and Technology Laboratory of Padjadjaran University, the DU145 and HEK-293 cell lines are the collection of the Cell and Molecular Biology Laboratory of Padjadjaran University, WST-8, PBS, Dulbecco's Modified Eagle Medium (DMEM) high glucose (Sigma), Fetal Bovine Serum (Sigma), Tripsin TrypLE (Gibco), Penicillin-Streptomycin (Sigma), Phosphate Buffer Saline 10X (Lonza).

Preparation of Test Materials

Preparation of Test Materials a-Mangsotin

The α-Mangostin used in this research is a collection from the Pharmacy and Pharmaceutical Technology Laboratory at Padjadjaran University, with a purity of <90%. In this study, the concentrations of α-mangostin used were 12.5 ppm, 25 ppm and 50 ppm.

Making Marine Mineral Concentrate Test Materials

The marine mineral concentrate used in this research is a collection from the Pharmaceutical and Pharmaceutical Technology Laboratory at Padjadjaran University. The Marine Mineral Concentrate comes from Pamekasan Madura with the sampling point being ± 500 – 750 m from the coastline, and the depth range is around 1-1.1 m. Sea water sampling is carried out at low tide so that it is easier to reach the specified location. After the sea water is taken, it is evaporated. The concentrations used in this research were 12.5 ppm, 25 ppm and 50 ppm.

In Vitro Activity Testing

Making Medium (100 ml Medium)

Then spray it with 70% alcohol, then put it in a water bath at a temperature of 37^0C maximum 2 minutes. After that, spray it again with 70% alcohol and put it in *Bio* Safety Cabinet (BSC). Then carry out the treatment, namely entering Dulbecco's Modified Eagle

Medium (DMEM) as much as 90 ml, *Fetal Bovine serum* (FBS) as much as 10 ml and *penicillin-streptomycin* (PS) 1 ml into the bottle. then homogenize with a pipette by moving up and down. Then spray again with 70% alcohol. After that enter *Dulbecco's Modified Eagle Medium (DMEM), penicillin-streptomycin* (PS) into the chiller and *Fetal Bovine serum* (FBS) in the freezer.

Culture Sel

Prepare DMSO and put 1 ml of media in the freezer until it freezes, then remove the cells to -80°C (Wait until they are liquid), then transfer 1 ml of cells to a 15 ml cup, then add 3 ml of media, centrifuge for 4 minutes then discard the media , suspended with 1 ml of media (homogenize by pipetting up and down), then put the media into the petri dish until it covers the surface of the dish, then put the cells into the media evenly and cover the petri dish then slide it right and left to make it homogeneous, then incubate media into the incubator for 24 hours.

Cytotoxic Activity Testing Using the WST 8 Method

The test material was tested against the DU145 & HEK293 prostate cancer cell lines using the method *WST-8*. Cell lines were cultured using *Dulbecco's Modified Eagle Medium* which contains 10% fetal bovine serum and 1% penicillin-streptomycin. Cells were seeded on 96-well plates plate and incubated for 24 hours at 37°C with CO levels2 5%. After that the culture medium was replaced with new one and samples were given with several variations in concentration, Cisplatin as a control and DMSO as a blank. After 24 hours, Wst-1 reagent was added and incubated for 2 - 4 hours. After that, the CCK-8 reagent was discarded and the absorbance was measured using *Tecan Infinite spectrophotometer (λ 450 nm).* Calculation of cell survival rate (*cell survival rate*) is calculated using the formula:

$$\text{Survival Rate (\%)} = \frac{Sample\ absorbance - Blank\ absorbance}{Absorbance\ Negative\ control - Blank\ absorbance} \times 100 \quad (1)$$

Data Analysis

Data shown are mean ± *standard error of mean* (SEM). Data is analyzed using software *GraphPad Prism* version 9.0.0. One-way analysis of variance (ANOVA) followed by Tukey's follow-up test was used to determine statistical significance. A P value <0.01 was considered significant.

Result and Discussion

In vitro testing was carried out using the WST-8 method. The WST-8 test is included in the colorimetric test for evaluating cell metabolic activity, which can also be used to see the survival rate of the cells being tested (Stockert et al., 2018). In this study, the cell line used was DU145. The DU145 cell line is a human prostate cancer cell line that is often used in prostate cancer research (Alimirah et al., 2006). This study used cisplatin as a control because cisplatin is a first-line treatment for prostate cancer that is used together with carboplatin and oxaliplatin (7,8) (Melawati et al., 2022). The mechanism of cisplatin is its ability to interfere with cell division and trigger cell death by forming cross-links with the guanine bases of the DNA double helix chain which causes DNA transcription and replication to be disrupted (9,10) (Hibatu Wafi & Abidin, 2023).

The survival rate value obtained will then be used to calculate the IC50 value for each sample tested (Permatananda & Pandit, 2023). The test samples used were Marine Mineral Concentrate, α-Mangostin and cisplatin. IC50 is a measurement used as the potential of a compound or substance to influence biological activity which can indicate the concentration of the substance needed to have an effect on 50% of the test material (Hoetelmans, 2017). The IC50 values obtained for each test material can be seen in Table I.

DU 145 Cancer Cell Line

Table I. Percentage survival rate of α-Mangostin and cisplatin against DU145 cells

Concentration (ppm)	%Survival Rate		
			α-Mangostin
10	82.39	107.00	97.83
5	50.33	84.28	92.95
2.5	52.34	57.36	58.47
α-Mangostin concentration	Combination of α-Mangostin & Sea Mineral Concentrate 12.5 ppm		
10	56.03	46.98	97.71
5	19.34	36.50	37.88
2.5	30.45	37.69	43.65
α-Mangostin concentration	Combination of α-Mangostin & Sea Mineral Concentrate 25 ppm		
10	17.95	33.86	45.70
5	9.00	39.91	18.97
2.5	35.65	49.70	36.24
α-Mangostin concentration	Combination of α-Mangostin & Sea Mineral Concentrate 50 ppm		
10	62.53	80.18	13.08
5	23.86	12.76	23.44
2.5	34.45	49.36	31.81
			Cisplatin
20	40.12	53.84	44.45
4	67.34	78.20	70.48
0.8	60.06	55.61	35.61

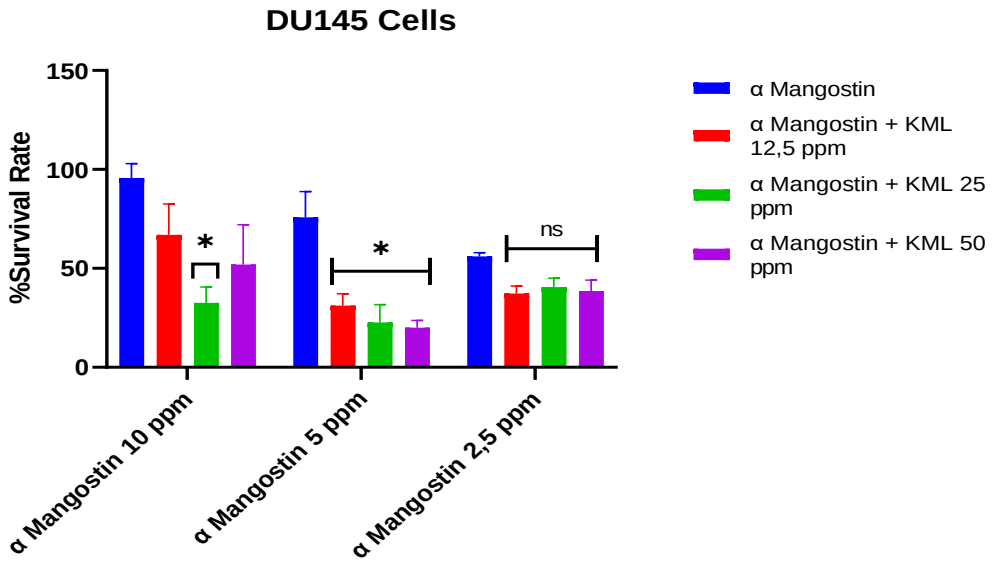

Figure 1. Statistical analysis of the survival rate of α-Mangostin alone and the combination of α-Mangostin + KML against the DU145 cancer cell line. Results were compared with α-Mangostin Single in each concentration group. *significantly different, ns is not significantly different.

The results of testing cytotoxic activity on DU145 cells in Table II show that the higher the concentration used, the higher the cytotoxic effect, which is indicated by the survival rate (Fujihara & Ukimura, 2022). The IC50 values of each test substance are α-Mangostin 16.89 ppm, cisplatin 4,649 ppm, α-Mangostin – KML 12.5 ppm 1,732 ppm, α-Mangostin – KML 25 ppm 4,930 ppm and α-Mangostin – KML 50 ppm 5,194 ppm. The survival rate test results showed that there was no significant difference between α-Mangostin and cisplatin and α-Mangostin – KML (Cannarella et al., 2021).

α-Mangostin provides inhibitory activity against the DU 145 cancer cell line in the active category (Xie et al., 2023). This is in accordance with previous research, where α-Mangostin showed good cytotoxic effects against the DU 145 cell line with an IC50 value (He et al., 2023). Value 20-100 µg/mL. Meanwhile, cisplatin is in the very active category. This study used cisplatin as a control because cisplatin is a very effective anticancer drug, the success rate of cancer therapy with cisplatin is proportional to the high dose given (Artayasa et al., 2023). However, its use is limited by its side effects on normal tissue (Mardhiyah & Yonata, 2015).

Magnesium is found in many marine minerals. Magnesium affects cell functions that are important for tumor growth and spread, such as proliferation and angiogenesis, and magnesium deficiency can trigger anti- and protumorogenesis effects (Trapani et.al., 2014). As a major mineral component, magnesium plays an important role in inhibiting metastasis, and magnesium and calcium deficiencies are associated with an increased risk of cancer and metastasis (Massa et al., 2014; Nasulewicz et al., 2004). In preliminary tests, it appeared that KML had good activity against normal cells, but was less effective against cancer cells (Alaydrus et al., 2021; Alaydrus et al., 2022). The research carried out a combination of KML with natural ingredients that have the potential to act as anticancer agents, one of which is α mangostin (Meylina et al., 2021).

HEK 293 Cell Line

Table 2. Percentage survival rate of α-Mangostin and cisplatin against HEK293 cells

Concentration (ppm)			%Survival Rate α-Mangostin
10	10.68	11.48	12.60
5	15.64	18.05	11.08
2.5	38.97	34.58	40.81
α-Mangostin concentration	Combination of α-Mangostin & Sea Mineral Concentrate 12.5 ppm		
10	60.67	61.74	70.85
5	48.17	68.23	58.13
2.5	68.23	79.35	78.91
α-Mangostin concentration	Combination of α-Mangostin & Sea Mineral Concentrate 25 ppm		
10	64.79	67.59	71.81
5	50.92	45.25	40.68
2.5	0.95	0.40	5.078
α-Mangostin concentration	Combination of α-Mangostin & Sea Mineral Concentrate 50 ppm		
10	47.32	69.92	67.33
5	45.72	46.74	48.35
2.5	1.09	0.26	0.11

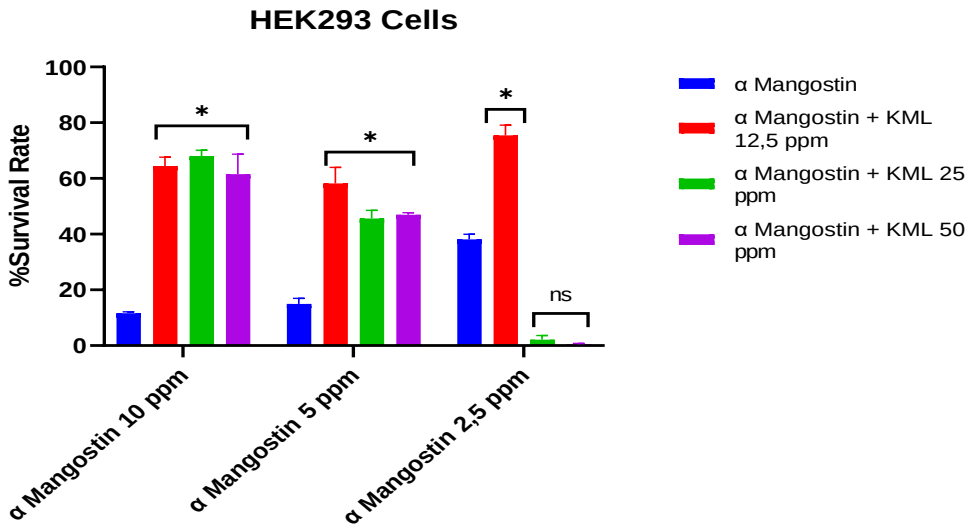

Figure 2. Statistical analysis of the survival rate for single α-Mangostin and the combination of α-Mangostin + KML against the normal cell line HEK 293. Results were compared with single α-Mangostin in each concentration group. *significantly different, ns is not significantly different.

The HEK 293 cell line is a normal cell line that has been used for many years for biological and technological research (Makhrus et al., 2021). HEK 293 has good growth which makes this cell line widely used in research but genes and proteins, as well as for testing the safety of a compound (Kavsan et al., 2011; Darsono et al., 2024). The IC50 value obtained for each test material can be seen in Table I. In contrast to the IC50 value for the DU145 cell line, for the HEK-293 cell line it is hoped that the sample will not affect the cell line, in other words, a greater IC50 result indicates a better effect (Damayanti & Yohandri, 2022). The smallest IC50 results were obtained by the cisplatin sample, which shows that cisplatin has the greatest effect on the HEK-293 cell line. On the other hand, the largest IC50 value was owned by the α-Mangostin – KML 12.5 ppm sample with a value of 1,732 ppm. In this case, α-Mangostin – KML 12.5 ppm is considered the best because it has the least effect on HEK-293 as normal cells (Khairi et al., 2023).

Marine mineral concentrate and α-Mangostin, have the potential to be developed as anticancer (Unterrainer et al., 2024). Next, a combination of marine mineral concentrates and α-Mangostin was tested, with the hope of reducing the survival rate of DU145 cells and increasing the survival rate of HEK-293 cells. The results of testing the combination of marine mineral concentrate and α-Mangostin on HEK-293 cells can be seen in Figure 2 (Fatmawati et al., 2021).

The results of the combination of sea mineral concentrations with α-Mangostin on HEK-293 cells can be seen in Figure 2, in the combination of KML 12.5 ppm– α-Mangostin 12.5 ppm, KML 25 ppm– α-Mangostin 25 ppm, and KML 50 ppm – α-Mangostin 50 ppm. This combination shows a very good survival rate and is significantly different when compared to a single sample of α-Mangostin (Liao et al., 2023). This confirms that a single sample of α-Mangostin can have a large cytotoxic effect on HEK-293 cells, and the addition of KML to α-Mangostin can significantly improve the effect of α-Mangostin by increasing the survival rate in normal HEK-293 cells (Takeuchi et al., 2022).

IC50 Cisplatin & α-Mangostin

Table 3. IC50 values of α-Mangostin and cisplatin

Compound	IC50 (Ppm)	Cytotoxic Activity*
α-Mangostin	16.89	Active
Cisplatin	4.64	Very active
α-Mangostin – KML 12.5 ppm	1.73	Very active
α-Mangostin – KML 25 ppm	4.93	Very active
α-Mangostin – KML 50 ppm	5.19	Very active

*Cytotoxic activity against cancer cells is divided into IC50 value ≤ 10 mg/L very active, IC50 value ≤ 10 – 100 mg/L Active, IC50 value > 100 mg/L less active

IC50 test results for Cisplatin and α-Mangostin in table 3. Shows that the higher the concentration used, the higher the cytotoxic effect, which is indicated by the % survival rate. IC50 value. Of each test ingredient, α-Mangostin 16.89 ppm, combination of α-Mangostin-KML concentration of 12.5 ppm, namely 1,732 ppm, combination of α-Mangostin-KML concentration of 25 ppm, namely 4,930 ppm, combination of α-Mangostin-KML concentration 50 ppm 5,194 ppm, and cisplatin 4,649 ppm (He et al., 2023). In Figure I, the results of the combination of sea mineral concentrations with α-Mangostin on DU145 cells showed a decrease in the survival rate. The results of data analysis showed significant differences for all samples (Rudiana et al., 2023).

The results of this study show that Sea Mineral Concentrate and α-Mangostin can complement each other in providing cytotoxic effects. Where α-Mangostin helps Sea Mineral Concentrate to increase the cytotoxic effect on DU145 cancer cells and Sea Mineral Concentrate helps reduce the cytotoxic effect of α-Mangostin on normal HEK-293 cells, this can be proven by the selectivity index results shown in table III.

Conclusion

The IC50 values of α-Mangostin and cisplatin against DU 145 cells were 16.89 ppm and 4.65 ppm. At a concentration of 12.5 pmm there was no significant difference between cisplatin and α-Mangostin. α-Mangostin helps sea mineral concentrate to increase the cytotoxic effect on DU 145 cancer cells and sea mineral concentrate helps reduce the cytotoxic effect of α-Mangostin on normal HEK-293 cells.

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Conceptualization; G.P.A.; methodology.; S.A.; validation; formal analysis; N.P.D; investigation.; S.A.; resources; S.A; data curation: N.P.D; writing—original draft preparation. G.P.A.; writing—review and editing: N.P.D; visualization: G.P.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest
The authors declare no conflict of interest.

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