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POTENTIAL OF BAROMA RICE AS ANTI-CANCER FOOD CANDIDATE VIA CELL CYCLE ARREST AND APOPTOSIS

POTENSI BERAS BAROMA SEBAGAI KANDIDAT MAKANAN ANTI KANKER MELALUI PENGHAMBATAN SIKLUS SEL DAN APOPTOSIS

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ABSTRAK

Kanker ditandai dengan sel-sel tubuh terus membelah tanpa kendali. Kanker sering terdeteksi ketika sudah memasuki stadium lanjut sehingga sulit untuk diobati. Beras merupakan makanan pokok yang banyak digunakan oleh lebih dari separuh penduduk indonesia. Posisi nasi yang merupakan makanan pokok dapat dijadikan terapi atau pengobatan yang baik untuk mengatasi meningkatnya jumlah kasus kanker. Beras dilaporkan memiliki banyak kandungan kimia yang bermanfaat. IC_{50} ekstrak etanol beras baroma adalah 316,01µg/ml. Beras baroma yang dimasak dengan kompor menunjukkan nilai IC_{50} sebesar 672 µg/ml sedangkan Beras yang dimasak magic com menunjukkan nilai IC_{50} sebesar 1232 µg/ml. Ekstrak beras baroma mentah dan dimasak dengan kompor tidak cukup kuat untuk memicu apoptosis pada sel kanker dan dapat menghentikan siklus sel pada tahap g1. Penelitian ini menunjukkan bahwa ekstrak beras baroma mempunyai sifat sitotoksik terhadap sel kanker usus besar Widr dan berbagai bukti lain mengenai keunggulan beras baroma, diharapkan beras ini dapat menjadi makanan yang dapat mencegah kanker usus besar.

Kata kunci: *antikanker; apoptosis; beras baroma; siklus sel; sitotoksik.*

ABSTRACT

Cancer is a condition where the body's cells continue to divide without control. Often, this cancer is detected when it has entered an advanced stage, making it difficult to treat. Rice is a staple food widely used by more than half of Indonesia's population. The position of rice, which is a staple food, can be used as a prospective treatment to overcome the increasing number of cancer cases, especially in cases of colon cancer. Rice is reported to have many beneficial chemical contents. In cytotoxicity testing using WiDr colon cancer cells, the IC_{50} of the ethanolic extract of baroma rice is 316.01µg/ml. Stovetop cooked baroma rice showed an IC_{50} value of 672 µg/ml, while magic com cooked rice showed an IC_{50} value of 1232 µg/ml. Raw and stove-cooked baroma rice extracts are not strong enough to trigger apoptosis in cancer cells and can arrest the cell cycle at the G1 stage. This research shows that baroma rice extract has cytotoxic properties against WiDr colon cancer cells and various other evidence regarding the advantages of baroma

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rice. It is hoped that this rice can become a food that can prevent colon cancer.

Keywords: *anticancer; apoptosis; baroma rice; cell cycle; cytotoxic.*

INTRODUCTION

Cancer is a disease caused by the uncontrolled growth of abnormal cells and can attack various parts of the body. These cancer cells can grow and spread to other parts of the body, which is known as metastasis, and that is why cancer is considered dangerous. Another thing that makes cancer considered dangerous is the relation between the success of its treatment and the number of cases of death. It is estimated that there will be 18.1 million new cancer cases worldwide in 2020 (Cancer Research UK, 2020). Several cancer factors explained are related to internal factors, known as hereditary factors, which are difficult to avoid.

Other things cause cancer coming from external factors, one of which is reported to have the highest incidence, such as unhealthy eating patterns. Several lifestyle trends that ultimately change activities and eating patterns have resulted in many new diseases, some of which are caused by the entry of many free radicals into the body. These free radicals come from the food consumed and accumulate more if not accompanied by healthier complementary foods or exercise (Kumar & Pandey, 2015).

In principle, cancer begins when the body's cells divide without control. Often, cancer is detected when it has entered an advanced stage, making it difficult to treat. All cell bodies can turn into cancer if they are exposed to a trigger to continue dividing. The case that is widely reported in Indonesia and is mostly related to changes in diet is colon cancer. Colon cancer ranks third in Indonesia and around 10% worldwide (Park & Jee, 2018).

Cancer treatment is often directed at surgery to remove the part of the body affected by cancer and is also accompanied by chemotherapy to remove the remaining cancer cells. Existing alternative treatments still have undesirable side effects for people living with cancer, such as hair loss and uncomfortable nausea and vomiting. Early detection and a healthy lifestyle, including good food, can prevent cancer. Diet has a big influence on a person's health status. Through a healthy and appropriate diet, it is hoped that we can reduce the risk of cancer.

For Indonesians, rice is a staple food widely used by more than half of the population. The position of rice, which is a staple food, can be used as a prospective treatment to overcome the increasing number of cancer cases. Rice is reported to have many beneficial chemical contents. The benefits of rice are not only in the grain but also in other parts. Rice has many variants, such as red, black, and white rice, which are the most widely used.

The main content of rice is almost 80% carbohydrates, which makes it the most popular staple food. Apart from carbohydrates, rice also contains protein, fiber, and vitamins. The content of rice that is also claimed to be beneficial and can prevent cancer is the resistant starch content in rice. Resistant starch cannot be digested in the digestive tract and will continue until it reaches the large intestine. The presence of resistant starch in the large intestine can become food for bacteria in the large intestine (Hutabarat et al., 2018). Magic com cooking increases fat and protein content, while stove cooking elevates calories, starch, and total sugar (Akmalia et al., 2024).

In some regions, rice is unique and is a characteristic of the region. One of the typical types of rice that is often processed into special foods is baroma rice. Baroma rice is in great demand because it is generally longer and slimmer than rice and is said to be healthier. Baroma rice can be an alternative diet for people living with diabetes because it can control blood sugar in people with prediabetes and type 2 diabetes (Rahim et al., 2020). Cooked baroma rice still contains soluble fiber that cleanses the digestive tract and prevents constipation. Compared with other types of rice, baroma rice contains lower lev-

els of arsenic and heavy metals, thereby reducing the risk of cancer (Hong et al., 2014). Baroma rice contains complex carbohydrates. Therefore, it can be a stable energy source for the body because it provides a feeling of fullness for a long time.

From the description above, baroma rice has great potential to be consumed as a staple food. It also has ingredients and health benefits, including preventing cancer cases. The cooking process can cause the nutrients in food to be lost or reduced. Indonesian people usually process rice in two ways: cooking rice with a stove steamer and using a com. With this background, there is a need for further studies regarding the potential of baroma rice as an anti-cancer food candidate and the different effects of cooking rice on cell cycle arrest and induction of apoptosis in cancer cells.

Materials and Method

Extraction of Baroma Rice

The ingredients used in making the extract are raw baroma rice, baroma rice cooked using a stove, and baroma rice cooked using a magic com. The maceration method is used to make extracts. 1kg of raw baroma rice is ground using a blender. Once smooth, the rice grains are macerated with ethanol solvent thrice for three days.

Meanwhile, cooked rice is processed first using a stove and Magic com, then the resulting rice cooked into rice is also macerated using ethanol solvent three times for 3 days. The maceration results are filtered and stored daily and then replaced with a new solvent. The filtrate is evaporated with a rotary evaporator and dried in a freeze-dryer. The extract test solutions were made in 6 series with concentrations of 15.625 µg/mL, 31.125 µg/mL, 62.5µ g/mL, 125 µg/mL, 250 µg/mL, and 500 µg/mL using DMSO cosolvent and RPMI media.

Cell Culture and Cytotoxicity test

Colon cancer WiDr (ATCC) cells were cultured in RPMI media supplemented with fetal bovine serum, penicillin, and streptomycin. Cell preparation is carried out by transferring cells from a liquid nitrogen tank into a sterile conical tube containing media, centrifuged at 600 rpm for 5 minutes, the supernatant is removed, and then new media is added, put into a CO_2 incubator at 37° C for 24 hours with 5% CO_2 flow, then the culture medium is changed and so on until confluent cells are obtained. The next step is harvesting by separating the media, washing the cells with PBS, adding trypsin-EDTA, and incubating for 3 minutes. Media is added, cells are resuspended and then transferred to a sterile conical tube. Cells are counted with a hemocytometer, and cells with the required concentration are made.

A cytotoxicity test is carried out by distributing 1 x 104 cells/well into 96 well plates, which are incubated for 24 hours. The media is taken, washed with PBS, and then added 100 µl of culture medium only (control) or sample, incubated for 24 hours. The culture medium containing the samples is discarded and washed with 100 µl PBS. Then 100 µl of culture medium containing 5 mg/ml MTT is added into each well and incubated at 37°C for 4 hours. The MTT medium is discarded, washed with PBS, and 200 µl of isopropanol acid solution is added. Shaken with a shaker for 10 minutes, then read with an ELISA reader at a wavelength of 550 nm.

Apoptosis Analysis

Observation of apoptosis due to extract treatment is carried out using the flow cytometry method. The flow cytometry procedure for detecting the first cells is that the cells are incubated for 24 hours. The cells were washed with buffered saline, suspended in the buffer with annexin v and propidium iodide for paint so that it mixes well vortexed, and incubated for approximately 10-15 minutes in the dark at room temperature. The cells are then ready to be analyzed using machine flow cytometry.

Cell Cycle Analysis

The observation of proliferation begins with harvesting cells, counting them, and diluting them with complete culture media so

that the number of cells transferred in the 96-well plate is 5x10 cells/well. Subsequently, various concentrations are added to the wells and incubated in a 5% CO_2 incubator at 37°C for 24 and 48 hours. After incubation, the medium is removed and added to each well 10µ MTT reagent (TACS MTT Cell Proliferation assay®4890-25Cat-K) with a 0.5 mg/ml concentration in the dark. It must be incubated at 37°C for 4 hours until formazan crystals are formed. Cell conditions are observed with an inverted microscope, and then formazan is eluted from cells with DMSO. The results are read using an ELISA microplate reader at an absorbance of 550 nm. Cell proliferation can be expressed as a percentage to describe how many cells undergo division or growth in a certain period. In flow cytometry, the percentage of proliferation can be calculated by comparing the number of cells in the active phase of division (S phase or M phase) with the total cells analyzed.

RESULTS AND DISCUSSION

Baroma rice used in this research is raw baroma rice and baroma rice that has been processed using a stove and magic com. The reason for using rice processed here is according to the habits of people who process rice using stoves and magic com. The aim of cooking rice using these two methods is to compare the effects on cancer cells, namely the induction of apoptosis and cell cycle arrest, between those cooked on the stove and magic com. Cooking using these two methods involves different temperatures, which is assumed also to affect the chemical content.

Cytotoxicity test

One approach to finding chemopreventive compounds is exploring natural materials, especially plants. Cytotoxicity test was performed against the WiDr cell to find cell growth inhibition potential due to the Baroma rice ethanol extract treatment. This test is done to determine the test sample level which can inhibit growth of WiDr cells up to 50% (IC50). In the test, a comparison of chemotherapy drugs that are often used is given, namely doxorubicin. Doxorubicin is the most commonly used chemotherapy drug (Kciuk et al., 2023). Chemotherapy is known to be one of the cancer treatments carried out in cancer cases, but unfortunately, chemotherapy using chemical drugs still has many side effects. Some of the effects of using doxorubicin that are detrimental to the body are Nausea and vomiting, diarrhea, loss of appetite, hair loss during treatment, fungal infections of the nails, and cancer sores or sores in the mouth.

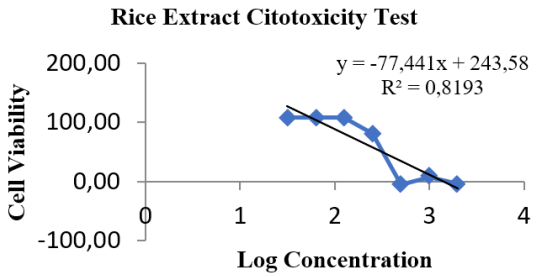

Figure 1.
Chart from Rice Extract Cytotoxicity Test
Source: Research documetation (2023)

From Table 1, it can be concluded that the cytotoxicity test results are expressed in IC_{50} values. The IC_{50} of the ethanolic extract of baroma rice is 316,01µg/ml. This result is higher than doxorubicin, which has an IC_{50} value (0,88 µg/ml). Even though it has a higher IC_{50} value, the cytotoxicity test results on the ethanolic extract of baroma rice are still moderately cytotoxic. Cytotoxicity can be grouped into 3, namely:

(1) potential cytotoxic if IC50<100µg/ml,
(2) cytotoxic moderate if 100µg/ml< IC50<1000µg/ml,
(3) non-toxic if IC50>1000µg/ml

(Fujiko et al., 2020)

Table 1.

Extract type	IC_{50} (µg/l)
Raw Baroma Rice	316,01 µg/ml
Stove-Cooking Baroma Rice	672 µg/ml
Baroma Rice Cook Magic com	1232 µg/ml
Doxorubicin	0,88 µg/ml

IC_{50} Value from Baroma rice extract cytotoxicity test
Source: Research documetation (2023)

Apart from looking at the cytotoxicity value of raw baroma rice, the cytotoxicity value of cooked baroma rice was also examined. There is a significant difference in the cytotoxicity test results of baroma rice cooked using a stove and cooked using a magic com. Stovetop-cooked baroma rice shows lower numbers when compared to magic-cooked baroma rice. The temperature difference in stove and magic com cooking is not very significant, namely 87.8°C and 87.9°C, respectively. Stovetop-cooked baroma rice showed an IC_{50} value of 672 µg/ml, while Magic Com-cooked rice showed an IC_{50} value of 1232 µg/ml. Stove-cooked baroma rice is the same as raw baroma rice, which has an IC_{50} below 1000 µg/ml, so it is still in the moderate cytotoxic category, while magic-cooked baroma rice has an IC_{50} figure above 1000, so it is in the non-toxic category.

Group compounds with potential cytotoxicity can be used as an anti-cancer agent. In contrast, cytotoxic moderate can be used for chemoprevention to prevent and inhibit cancer growth. Compounds possessing anticancer potential are expected to suppress or inhibit the rate of cancer growth and reduce the side effects of chemotherapy. Rice, a staple food for the Indonesian population, is expected to become a healthy diet and prevent cancer, more specifically colon cancer.

In this research, the compound content of baroma rice has not been tested. In previous studies, various types of rice generally contain flavonoids. Rice contains polyphenolic antioxidants, where anthocyanins are part of a group of compounds, namely polyphenolates. Apart from that, various types of rice also contain tannin (Oktaviani et al., 2019). Cancer cells are the uncontrolled proliferation and dedifferentiation of normal cells. Cancer, a very serious problem in the human metabolic syndrome, is a major cause of death and morbidity worldwide. The presence of antioxidants, especially flavonoids, is thought to be able to be a chemotherapy agent.

Figure 1 shows the cytotoxicity test results on WiDr cancer cells treated with baroma rice extract, and the data is processed in a graph. The ethanolic extract of baroma rice has moderate cytotoxic potential due to its flavonoid content. The content of metabolites secondary to the plant influences the plant's pharmacological ability. A secondary metabolite is not a primary metabolite, but a unique compound obtained from the metabolism of primary metabolites in specific pathways. Secondary metabolites are expected to control the cell replication process in cancer cells and trigger apoptosis, so apoptosis and cell division mechanisms were tested further. Based on the cytotoxicity test results where the IC_{50} results were below 1000 µg/ml, namely raw baroma rice extract and stove-cooked baroma rice, these two extracts were then continued with apoptosis and cell cycle tests.

Apoptosis Test

To control cancer cells, cells can undergo apoptosis to reduce the number of cells that continue to grow. Natural compounds that can be used as medicine or cancer prevention are expected to have the ability to trigger apoptosis to maintain body homeostasis. Another death mechanism that can be experienced by cancer cells is necrosis. Observing the apoptosis test this time, we can see the number of cells that experience death through apoptosis and necrosis. The test results can be seen in Table 2 and Table 3. Table 2 and Figure 4 are the results of the apoptosis test on raw baroma rice extract, and Table 3 shows the results of the apoptosis test on baroma rice extract cooked using a stove.

Table 2.
Apoptosis percentage of Baroma Rice Extract

Treatment	Cell Percentage (%)			
	Living cells	Early Apoptosis	Late Apoptosis	Necrotic cell
cell control	92.10	1.10	6.00	1.00
IC_{50}	88.90	0.90	8.30	2.10
1/2 IC_{50}	91.50	1.00	4.60	3.10
Doxo	0.80	0.40	8.40	90.60

Source: Research documetation (2023)

Flow cytometry test can distinguish apoptotic or necrotic cells based on the ability of Annexin V, an intracellular annexin member, to bind to Ca_2^{+-} dependent phosphatidylserine. Under normal conditions, Phosphatidylserine is only present in the intracellular layer of the plasma membrane of healthy cells. If early apoptosis occurs, membrane asymmetry is lost, and phosphatidylserine is translocated to the external layer of the cell membrane (Lapenna & Giordano, 2009). Labeled Annexin V fluorochrome is used to detect this target. Annexin V cannot tell the difference between apoptotic and necrotic cells; to help differentiate them, Propidium Iodide (PI) is used.

The early phase of cell apoptosis does not react with PI, whereas in late-phase apoptosis, cells will be stained by PI because this dye will penetrate the nucleus and bind to DNA. Propidium iodide is a dye fluorescently bonded to DNA, when excited at a wavelength of 488 nm laser light, will be detectable which is used to evaluate living cells or cells that still contain DNA in the cell cycle being analyzed by flow cytometry (Ormerod, 2006). In the results of the apoptosis test for raw baroma rice extract using the IC_{50} dose, it was seen that the cells in the early apoptotic stage were 0.9%, the cells in the late apoptotic stage were 8.30%, and the cells that experienced death by necrosis were 2.10%. Cells in the late stage of apoptosis were almost the same as the results using doxorubicin, but the cells that experienced death by necrosis were greater on doxorubicin.

In the apoptosis test using stove-cooked baroma rice extract, the number of cells that experienced apoptosis was smaller than the cells that experienced apoptosis when treated with raw baroma rice extract. Cells entering the early stage of apoptosis in the treated IC_{50} dose of cooked baroma rice extract were 0.90%, and cells entering late apoptosis were 4.50%. From the results of the apoptosis test, it can be seen that the baroma rice extract is less able to trigger apoptosis in widr cancer cells.

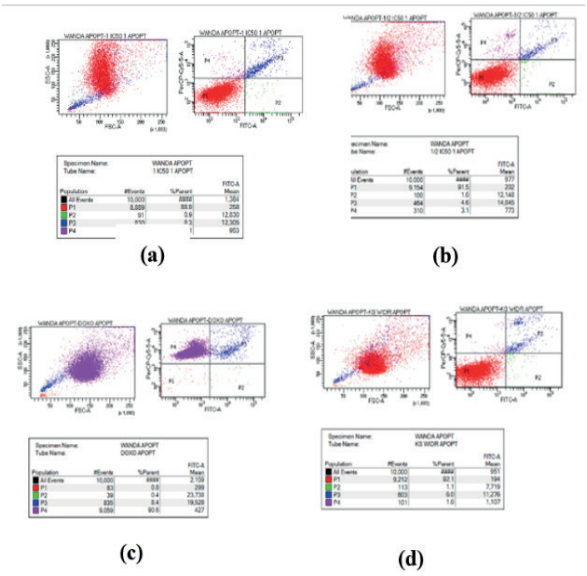

Figure 4.
Apoptotic Test from Baroma Rice Extract
(a) IC_{50} (b) ½ IC_{50} (c) Doxo (d) Control
Source: Reasearch documentation (2023)

One of the ingredients in baroma rice that could trigger apoptosis is flavonoids. Based on theory, flavonoids can stimulate apoptosis through several mechanisms, including inhibition of dna topoisomerase I/ II, modulation of signaling pathways, decreased expression of the bcl-2 and bcl-xl genes, increased expression of bax and bak (Ren et al., 2003).

Genes and activation of endonucleases enzyme topoisomerase is an enzyme that functions to cut dna entangled due to double opening strands of dna by the enzyme helicase, rewind, and then reconnect. The enzyme works on extending dna replication. If the enzyme activity of topoisomerase is inhibited, then stabilization of the dna topoisomerase complex will be truncated so that it produces permanent double-strand breaks in dna. Damaged dna will activate p53 and trigger the onset of apoptosis (Beck et al., 2001). The necrosis results in this test can also be caused by a long incubation period (24 hours) so that the apoptotic phase has passed.

CELL CYCLE TEST

Cancer cells fail in the regulatory mechanisms for cell multiplication. Cells that experience DNA damage will continue to divide and fail in the checkpoint mechanisms in the cell cycle that should be able to regulate cell homeostasis. The cell cycle process is important because protein and RNA synthesis decreases abruptly during the mitotic phase (M phase), and division occurs between two cells. After that, the cell can enter an interphase to re-enter the rest phase (G0). Cells in the G0 phase still have the potential to proliferate clonogenic or stem cells (stem cells) that can increase the number of cancer cells, which are cells that are in the proliferative cycle and the G0 phase. The cell cycle test results can be seen in Table 4 and Figure 5 for testing raw baroma rice extract and Table 5 for testing baroma rice extract cooked using a stove.

Table 4.
Cell Cycle of Baroma Rice Extract

Treatment	Cell Percentage (%)		
	G0/G1 Phase	S Phase	G2/M Phase
cell control	73.20	11.50	15.00
IC_{50}	71.20	11.80	16.70
1/2 IC_{50}	72.10	11.40	16.10
Doxo	65.90	16.50	17.00

Source: Reasearch documentation (2023)

Table 5.
Cell Cycle Cooked Baroma Rice Extract on Stove

Treatment	Cell Percentage (%)		
	G0/G1 Phase	S Phase	G2/M Phase
cell control	73.20	11.50	15.00
IC_{50}	67.70	11.00	19.60
1/2 IC_{50}	72.50	10.50	16.70
Doxo	65.90	16.50	17.00

Source: Reasearch documentation (2023)

In the cell cycle test results of Baroma rice extract, it was seen that many cells accumulated in the G1 phase. All results on extracts, control cells, and doxorubicin show the same results. Many cells are in the G1 phase. This shows that the compounds in Baroma rice extract can withstand the cancer cell cycle. Compounds contained in black rice extract are thought to increase levels of cyclin A, and cyclin B. Vitamin E can increase the production of the cytokine IL-2 by naive T cells. IL-2 is a growth factor for immunocompetent cells that can increase the concentration of D2, E, and A cycles, which play an important role in the cell cycle (Adolfsson et al., 2001). After passing through the S phase, cyclin A will release Cdk2 and bind Cdk1, causing chromatin condensation needed for cell division (Lapenna & Giordano, 2009). Entering the M phase, cyclin A will be degraded, and cyclin B will have increased expression, which will bind Cdk1. The cyclin B1 and B2 complex with cdk1 is an M phase component or maturing factor (MPF), which regulates the process of spindle thread formation and sister chromatid pairs. Explained that cyclin B increases during the cell mitosis phase. The cyclin B1/Cdk1 complex will stimulate mitosis and play an important role in controlling microtubule rearrangement during mitosis (Pines & Hunter, 1990)

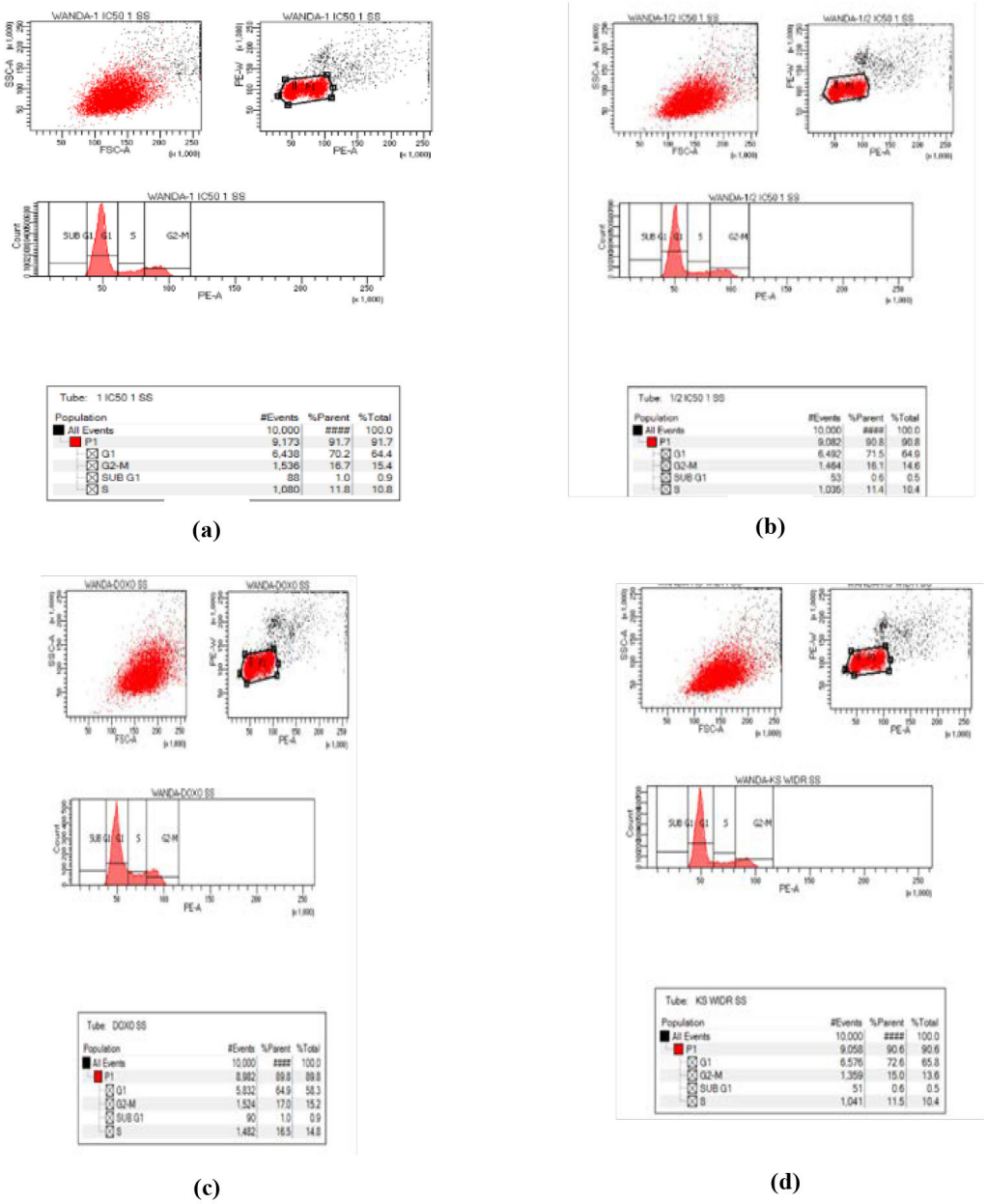

Figure 5.
Cell Cycle Test from Rice Extract
(a)IC_{50} (b) ½ IC_{50} (c) Doxo (d) Control
Source : Reasearch documentation (2023)

Further research is needed regarding the content of baroma rice and its more detailed effects. Baroma rice grains contain around 0.009 ppm of aroma compounds, 12 times more than non-baroma rice (Wasan et al., 2022). Exploration also needs to be strengthened regarding various types of Janis baroma varieties because apart from its natural location in India and Pakistan, there are also crossbreed baroma rice. Baroma rice cultivated in Pakistan and India, as well as some crossbreeding baroma rice, only have small physical differences; differences also occur in the aroma, where native baroma rice from India will have a strong aroma but weak if it is from crossbreeding (Kamath et al., 2008).

Baroma rice has a low glycemic index, so it is also safe for people with diabetes; its glycemic index is classified as moderate, ranging between 52-68. Another advantage of this rice is that it is rich in micronutrients such as iron and zinc (Mahajan et al., 2018). Natural antioxidants in baroma rice, such as polyphenols and flavonoids, reduce the incidence of degenerative diseases such as diabetes, cancer, cardiovascular disease, and aging. In terms of different types, both white and red baroma rice have a low glycemic index and do not change much after cooking (Somaratne et al., 2017). The fiber content in baroma rice is also very helpful in the digestive process. This fiber can prevent the formation of cancer cells (Bhat & Riar, 2015). With this research showing that baroma rice extract has cytotoxic properties against wider colon cancer cells and various other evidence regarding the advantages of baroma rice, it is hoped that this rice can become a food that can prevent colon cancer.

CONCLUSION

In conclusion, the IC_{50} of the ethanolic extract of aroma rice is 316.01µg/ml. Stovetop-cooked aroma rice showed an IC_{50} of 672 µg/ml, while Magic Com-cooked rice showed an IC_{50} of 1232 µg/ml. Raw and stove-cooked aroma rice extracts are not strong enough to trigger apoptosis in cancer cells but can arrest the cell cycle at the G1 stage. This research shows that aroma rice extract has cytotoxic properties against WiDr colon cancer cells.

Further analysis of the differences in specific chemical content in raw basmati rice and stove-cooked baroma rice is needed. It is also necessary to analyze at the fraction level and test the types of proteins that play a role in cancer cell apoptosis.

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