RESEARCH ARTICLE

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GLUT5, GLUT7, and *GLUT11* expression and *Bcl-2/Bax* ratio on Breast Cancer Cell Line MCF-7 Treated with Fructose and Glucose

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Abstract

Objective: Fructose and glucose are types of sugars commonly found in the diet that have been linked to cancer development. Glucose transporters (GLUTs) are facilitating the uptake of these hexoses. Expression of *GLUT5* is higher in cancer cells than in healthy tissue. *GLUT7* and *GLUT11* facilitate the transport of glucose and fructose; however, their expression in breast cancer has not been extensively studied. The *Bcl-2* family has been known as a regulator of the cell's survival and death. Here, we investigated the effect of the fructose-glucose combination in MCF-7 breast cancer cells on the viability, migration, and expression of *GLUT5*, *GLUT7*, *GLUT11*, and *Bcl-2/Bax* ratio. **Methods:** Breast cancer cells MCF-7 were treated with fructose, glucose, and combinations of fructose:glucose (75%:25%, 50%:50%, 25%:75%). Cell viability was assessed using an MTT test. Cell migration was examined with a wound-healing assay. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was performed to evaluate the mRNA expression of *GLUT5*, *GLUT7*, GLUT11, and *Bcl-2/Bax*. **Results:** The viability and migration of MCF-7 breast cancer cells elevated when treated with a combination of fructose and glucose, and glucose alone, compared to fructose alone. The expression levels of *GLUT5* and *GLUT7* were highest in combination of fructose:glucose (75%:25%). Conversely, the expression of GLUT11 was consistently low across all treated media. The highest *Bcl-2/Bax* ratio was shown in fructose:glucose combination (25%:75%). **Conclusion:** The viability, migration, and *Bcl-2/Bax* ratio are enhanced in the combination media with higher glucose. In contrast, when the fructose composition was higher in the media, expression of *GLUT5* and *GLUT7* increased.

Keywords: Breast cancer- MCF-7- hexoses- *GLUT5- GLUT7- GLUT11- Bcl-2- Bax*

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Introduction

One of the cancer cell's hallmarks is altered in metabolic regulation (Schiliro and Firestein, 2021). Cancer cells can adapt through complex metabolism related to genetic factors and the nutrients in the microenvironment (Elia and Haigis, 2021; Grasmann et al., 2021). Cancer cells consume high amounts of glucose to maintain cell proliferation (Jiang, 2017).

Apart from D-glucose, D-fructose is also a critical monosaccharide for the growth of cancer cells (Nakagawa et al., 2020). Foods high in fructose can cause increase the risk of several types of cancer and tumor progression (Charrez et al., 2015; Das, 2015; Hsieh et al., 2017; Weng et al., 2018). Fructose metabolism in cancer cells contributes to the Warburg effect by increasing glycolysis through the production of lactic acid (Nakagawa et al., 2021), which also stimulates the development and metastasis of breast cancer (Jiang et al., 2016). Substituting glucose with fructose as the energy source in MDA-MB-468 breast cancer cells induced an aggressive phenotype characterized by enhanced migration and invasion capabilities (Monzavi et al., 2010). Another study revealed that high fructose concentrations contribute to the advancement of colorectal cancer growth (Shen et al., 2022).

Glucose and fructose are transported into the cell by glucose transporters (GLUTs) (Shin and Koo, 2021). Cancer cells show high expressions of *GLUT5*, which is the main fructose transporter and also related to breast cancer prognosis (Koltai and Fliegel, 2023; Rana et al., 2023). *GLUT7*, on the other hand, is still controversial

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about the ability of which sugars it transports. Ebert et al., 2017 reported that *GLUT7* neither transports fructose nor glucose. Another study showed that *GLUT7* levels increased when fructose was applied to the Caco-2/TC-7 cell monolayer (Gauer et al., 2018). Another glucose transporter, *GLUT11* has the highest similarity to fructose transporter *GLUT5* (42% sequence homology), and facilitates the transport of both fructose and glucose (Navale and Paranjape, 2016; Holman, 2020). Since fructose and glucose play a significant role in the progression of cancer cells, GLUTs expression should be investigated further.

Despite its role in promoting the Warburg effect and sustaining the viability of cancer cells, fructose exposure has been found to induce apoptosis in non-cancerous cells (Jaiswal et al., 2015). Therefore, it is important to conduct a further examination of fructose's contribution to the apoptosis process. The B-cell lymphoma 2 (*Bcl-2*) family is known as regulators of survival and cell death divided into two groups, which are pro-apoptotic and anti-apoptotic (Adams and Cory, 2018). An increase in the *Bcl-2/Bax* ratio is associated with resistance to paclitaxel (Sharifi et al., 2014). This study aimed to investigate the viability, migration, and expression of these transporters and their impact on the *Bcl-2/Bax* ratio in MCF-7 breast cancer cells treated with fructose and glucose alone or in combination.

Materials and Methods

Cell culture

Sugar-free Dulbelcco's modified Eagle medium (DMEM) from GIBCO was used to prepare the cell culture media. Corresponding to the concentration of glucose standard cell culture medium formulations, all media's final concentration of hexose was 25 mM. As a carbon source, test media contained: fructose alone, fructose:glucose combination (75%:25%, 50%:50%, 25%:75%), and glucose alone, supplemented with 10% fetal bovine serum, L-glutamine from glutamax (4 mM), penicillin/ streptomycin (2 mM), and amphotericin-B (2 mM). Cells were cultured in a humidified incubator with 5% CO2 at 37°C.

Cell viability test

MTT assay evaluated cell viability after 24, 48, 72, and 96 hr. Briefly, cells were seeded at 5 x 103 in each well into a 96-well plate, and test media with fructose or glucose alone and combined were treated with three replicates. After the incubation, the medium was discarded and washed, then 20 µl MTT was added and incubated at 37°C for four hours. After solubilizing with 200 µl SDS, the absorbance was measured at 570 nm using a microplate reader.

Wound healing assay

Cells were seeded onto 24-well plates with a 5 x 104 cells/well density. After cells reached 80-90% confluence, a scratch was made with a 20-200 µl sterile pipette tip, generating approximately 1 mm width of cell-free area. After removing the cellular debris by gently washing it with PBS, pictures were taken (0 hr). Then, the culture media was replaced with the medium containing fructose and glucose, alone or in combination. At 6 hr post-wounding, an inverted microscope was utilized to capture post-treatment pictures (five independent, random fields). ImageJ software was used to analyze and calculate the gap size.

RNA extraction and quantitative polymerase chain reaction (qPCR)

Total RNA was isolated from cells using TRIzol reagent according to the manufacturer's instructions. RNA concentration was determined with a spectrophotometer (OD: 260nm) to synthesize cDNA with an iScriptTM cDNA synthesis kit (Biorad). The primer sequences are listed in Table 1, with *ß-actin* used as the reference gene. qPCR was performed in 10 µl reaction volume, with 5 µl 2X SensiFAST SYBR Green PCR master mix and 1 µl of specific primer set. The qPCR was performed at 95oC for 15 min, followed by 40 cycles of 94oC for 15 sec, 53oC for 30 sec, and 72oC for 30 sec. Each sample was examined in triplicate. Relative gene expression was calculated by the Livak method (Livak and Schmittgen, 2001).

Statistical analysis

All quantitative data are presented as mean ± standard deviation (SD) from three independent experiments. Significant difference among the group was assessed by One-way analysis of variance (ANOVA) and post hoc Tukey's test, with $P<0.05$ considered statistically significant.

Results

More glucose in media resulted in enhanced MCF7 viability

Viability cell was measured at 24, 48, 72, and 96 hr after cultured in media supplemented with fructose alone, glucose alone, or combination of both hexoses. The results showed that cell viability was greater in cultures treated with a combination of both hexoses compared to those treated with fructose alone.

The results shown in Figure 1, after 24, 48, and 72 hr, demonstrated a similar pattern, cells treated with glucose alone had the highest cell viability. The treatment with 50:50 of fructose and glucose exhibited the highest levels after 96-hour treatment. However, after incubation at all times, cells treated with fructose alone retained the lowest viability.

Fructose-glucose combination affected cell migration

Migration assay was analyzed by measuring the percent wound closure using ImageJ software (Figure 2). Cells cultured with fructose and glucose alone or combined media had a significantly higher percentage of wound closure than the control group. However, the combination media with an equal or higher glucose content (fructose:glucose 50%:50%, 25%:75%) and glucose alone had a significantly higher percentage of wound closure than the combination media with a higher fructose content and fructose alone. This result represented a higher

Table 1. Primer Used in qPCR

Gen	Primer Forward	Primer Reverse
GLUT5	5'-CCTTTGGGTCATCCTTCCA-3'	5'-ACAGACCACAGCAACGTCAA-3'
GLUT7	5'-TCGGTGCCTACAGTTTCATC-3'	5'-AATGCGGTTTATCTCCACAA-3'
GLUT11	5'-CGTGATGGGACAGGTGGT-3'	5'-GCTTTCAGGGAGCAGAGG-3'
Bcl-2	5'-CCGGAGAACAGGGTATGATA-3'	5'-TCAGGCAAGGAAGAAGATGC-3'
Bax	5'-GGAGACACCTGAGCTGACCTTG-3'	5'-CTGCCACACGGAAGACCTC-3'
ß-actin	5'-CGCGAGTACAACCTTCTTGC-3'	5'-ATACCCACCATCACACCCTGG-3'

migration rate observed when the cells were exposed to a higher concentration of glucose than an excessive concentration of fructose in the media. After 24 hr, the gap in all cell culture experiments was closed, except control without fructose and glucose.

GLUT level and Bcl-2/Bax ratio

The cell was cultured with fructose, glucose, and a combination of both for 72hr, and mRNA levels of *GLUT5*, *GLUT7*, and *GLUT11* were measured by RT-qPCR. Data was calculated and represented by relative quantitative.

The greatest fold change for *GLUT5* and *GLUT7*, as shown in Figure 3 was obtained at combination fructose:glucose (75%:25%). Meanwhile, *GLUT11* showed the lowest expression in all experiment media. In media with fructose alone, the mRNA expression of *GLUT5*, *GLUT7*, and *GLUT11* was lower than in the control medium without glucose and fructose. The same pattern was also shown in the culture with media combining fructose:glucose 25%:75%. In media with glucose alone, *GLUT5* had a slight increase in expression but was not applied for *GLUT7* and *GLUT11*. Interestingly, in the combination media fructose:glucose

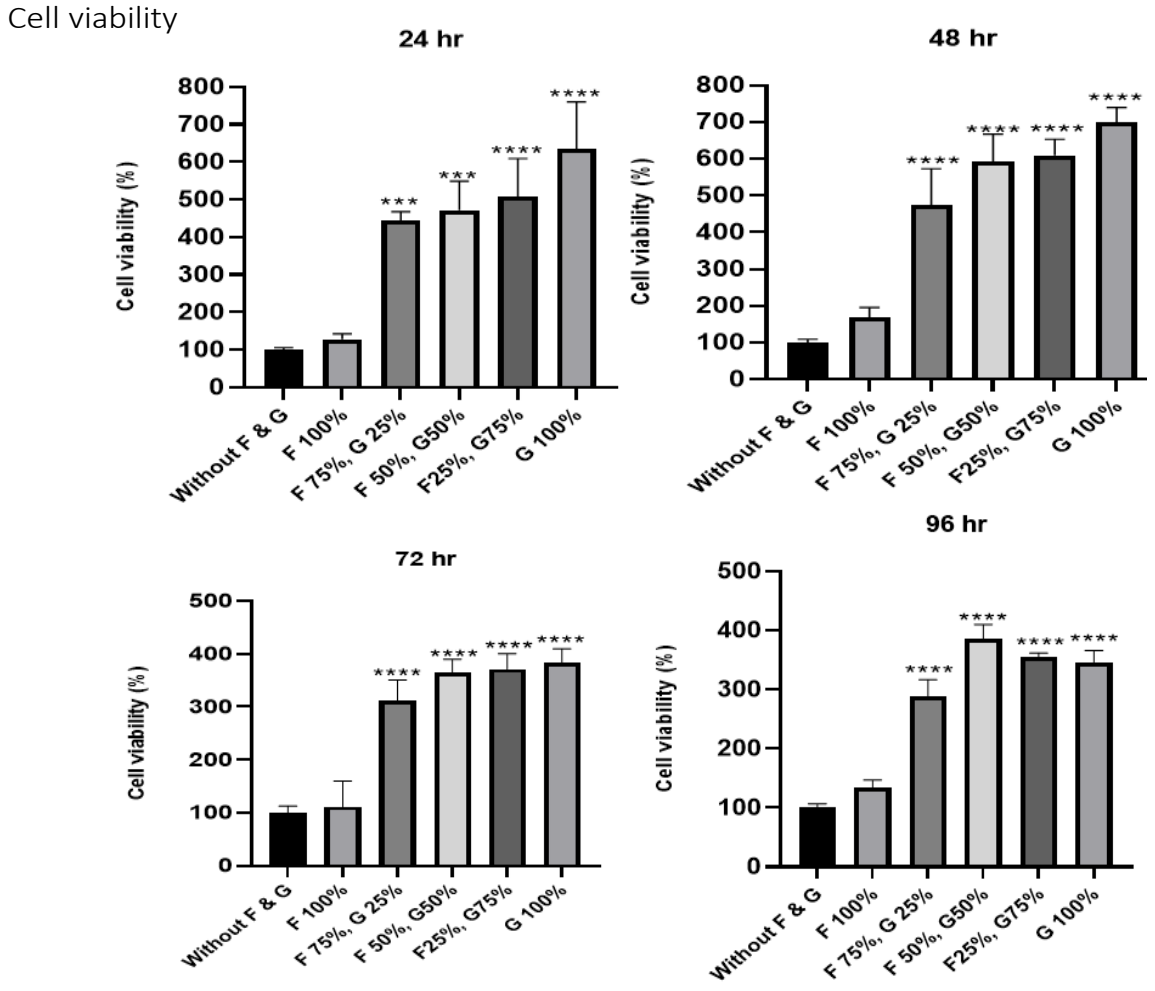

Figure 1. Effect of Various Combinations of Fructose and Glucose Supplemented in Growth Media on MCF-7 viability after 24, 48, 72, and 96 hr with MTT Assay. Viable cells percentage was calculated as follows: (absorbance of test media cell - absorbance of control media) / (absorbance of control cell - absorbance of control media) x 100%. Results are presented as mean ± SD (n=3). The stars indicate a significant difference compared with cells treated without fructose and glucose. ****P<0.001; F, Fructose; G, Glucose

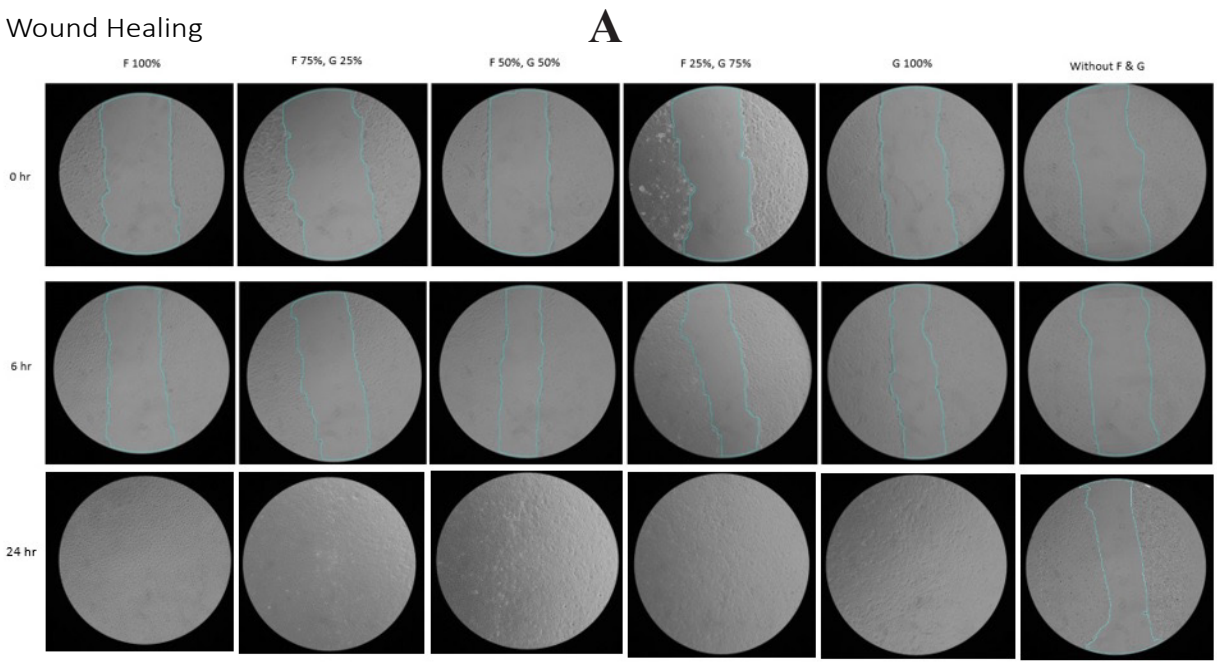

Figure 2A. Free Area Analysis According to MRI Tools Using ImageJ Software. (A) Pictures taken of wound healing assay at 0 hr, 6 hr and 24 hr after scratch, free area shown inside the blue line

75%:25%, the expression of *GLUT5* and *GLUT7* increased significantly.

Finally, the expression of *Bcl-2* and *Bax* was measured with RT-qPCR, as presented in Figure 4. For Bcl-2, cells treated with 100% glucose showed the highest fold change (~2). Wherewith *Bax*, the expression displayed all below to the control. For the *Bcl-2/Bax* ratio, the combination of fructose:glucose (25%:75%) has the highest ratio. The 100% fructose group and the combination of fructose: glucose (75%:25%) showed a lower *Bcl-2* and *Bax* expression than the control group, as did the ratio values.

Discussion

In this study, we have shown that the combination of fructose and glucose affected the viability and migration of breast cancer cells. The higher the percentage of glucose in the combination media, the greater the cell viability.

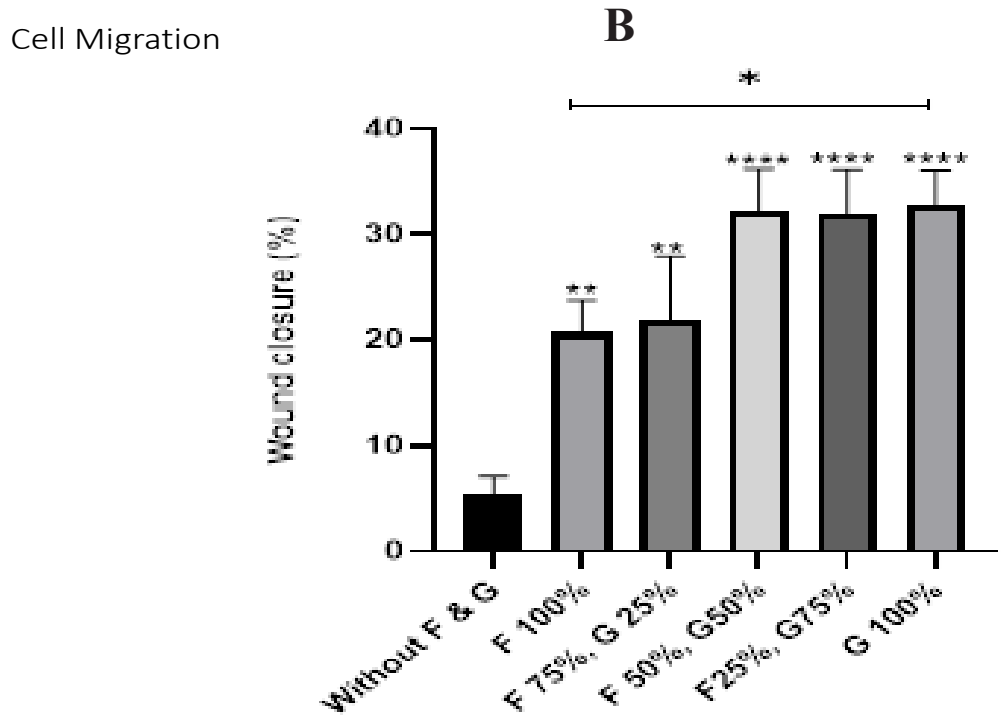

Figure 2B. Shows Quantitative Analysis Graph for Cell Migration. Wound closure was calculated by: free area from 6 hr minus free area form 0 hr (measured from five different field/well), with three replicates for each test. Data were expressed as mean ± SD. F, Fructose; G, Glucose

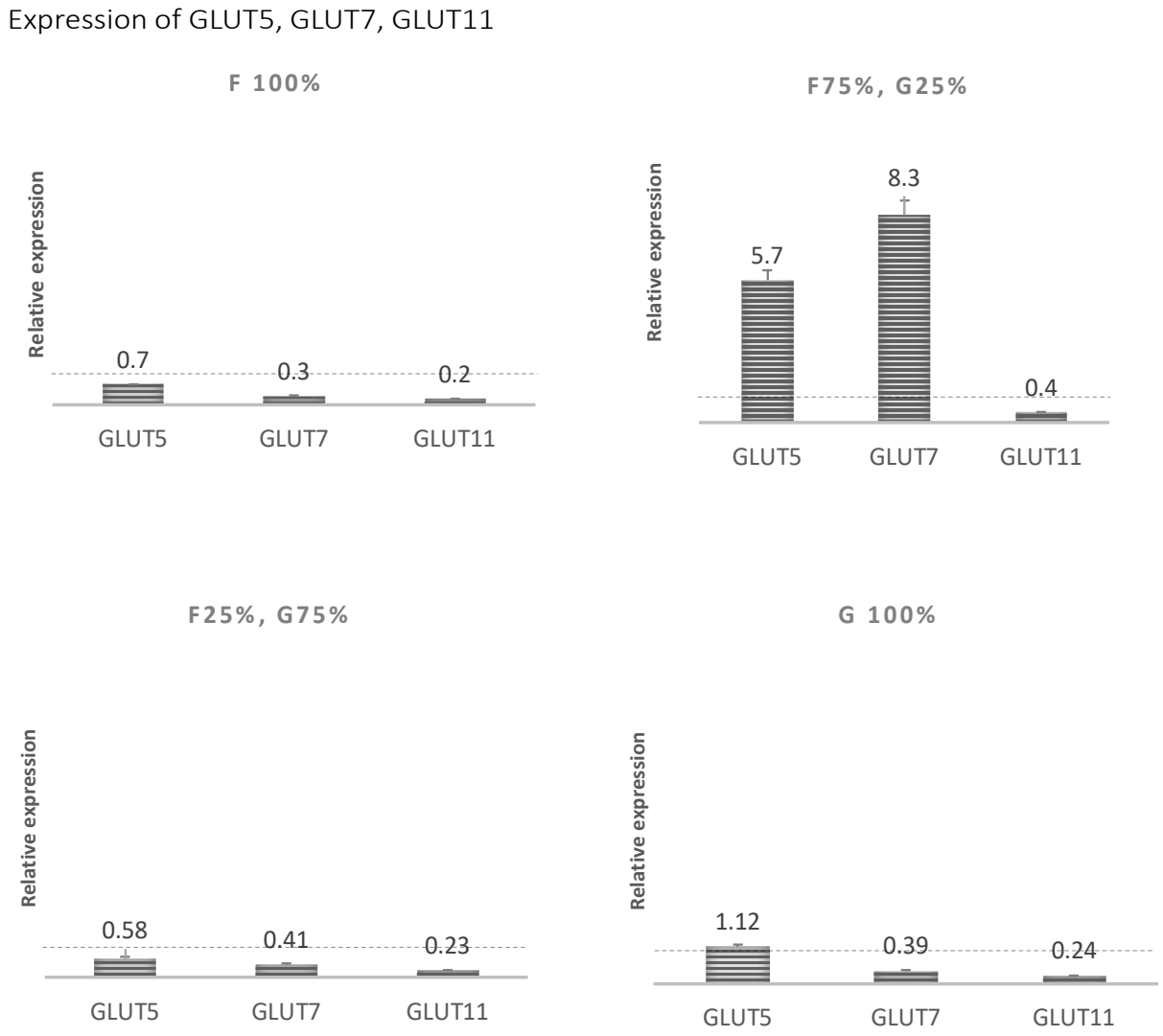

Figure 3. Relative mRNA Expression of *GLUT5, GLUT7*, and *GLUT11* for Each Experiment. Relative mRNA expression calculated with 2ΔΔCT method. Data were expressed as mean ± SD from three independent test. Controls are shown with dotted lines. F, Fructose; G, Glucose

This result confirmed that breast cancer cells, especially MCF7, depend on glucose as their glycolytic substrate to support viability. It was also shown that when these cells were grown in media with glucose alone, they consistently had the highest viability compared to other media groups. Meanwhile, cells grown in media with fructose alone had viability that was not significantly different from control media (without glucose and fructose). The last result was different from the results of a previous study (Fan et al., 2017) on MFC7 and MDA-MB, which found that the survival of these two cells cultured with 10 mM fructose-supplemented media was almost similar to 25 mM glucose-supplemented media and significantly higher compared to culture without glucose. However, another study on Jurkat cells (a lymphoblastic leukemia cell model) showed that 10 mM fructose induced cell death through elevated production of superoxide and hydrogen peroxide due to increased fructose oxidation through the oxidative phosphorylation pathway (Diaz et al., 2016). So, further studies are needed to explain at what levels of fructose inhibit cell viability or induce apoptosis or, conversely, strengthen cancer cells' survival by inhibiting the tricarboxylic acid cycle, which preserves the Warburg effect. The migration capacity of breast cancer cells in this study, as represented by the percentage of wound closure after 6 hours, showed results that aligned with the cell viability.

Glucose transporters have unique monosaccharide sensing and response abilities, as well as their cell-specific expression. Studies have indicated that breast cancer cells exhibit overexpression of glucose transporters, including GLUT1, GLUT3, GLUT4, and GLUT12, which play crucial roles in metabolism and the uptake of hexose molecules (McBrayer et al., 2012; Reinicke et al., 2012). A previous study indicated that *GLUT5* is not over-expressed in breast cancer cells or tissue (Gowrishankar et al., 2011). In a recent study, the participation of GLUT-2 as a fructose transporter in breast cancer was discovered (Hamann et al., 2018). The current study observed that MCF7 cells showed a higher *GLUT5* expression pattern compared to *GLUT7* and *GLUT11* when cultured in fructose and glucose alone, and in combination media with a greater percentage of

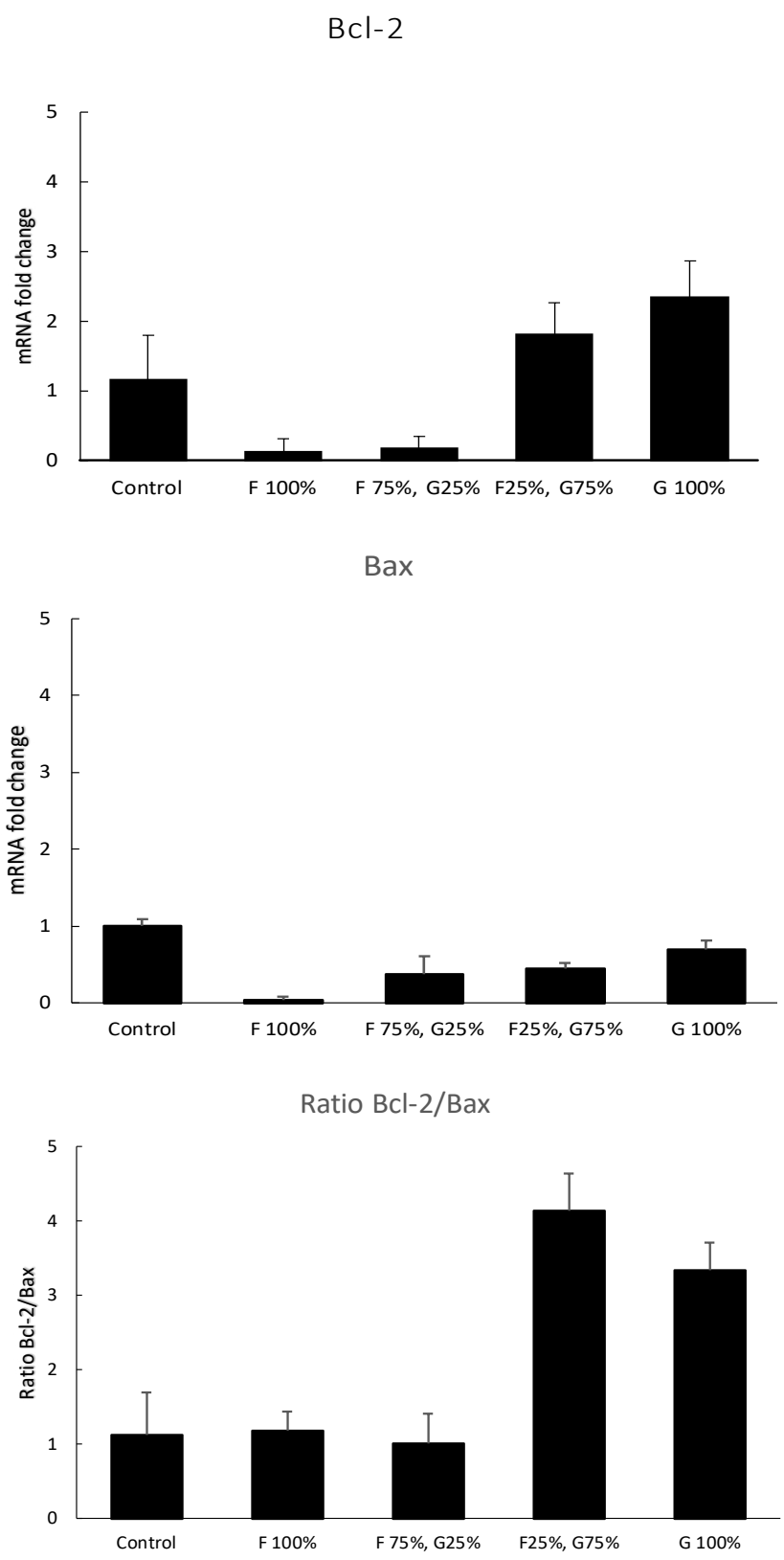

Figure 4. Expression of *Bcl-2, Bax* and Ratio of *Bcl-2/Bax* in Breast Cancer Cell MCF-7 Treated with Various Combinations of Fructose and Glucose. F, Fructose; G, Glucose

glucose than fructose. However, the expression levels of these three genes were lower than the control. These results indicate that *GLUT5*, *GLUT7*, and *GLUT11* are not the primary transporters for fructose and glucose in breast cancer cells. However, at a percentage of fructose greater than glucose (75%; 25%), there was an increase in *GLUT5* and *GLUT7* mRNA expression, with *GLUT7* being higher than *GLUT5*. These results can be initial

data that *GLUT5* and *GLUT7* most likely play a role in transporting glucose and fructose into breast cancer cells at certain concentration combinations of these two hexoses. This notion requires further proof with more advanced techniques because this study did not measure other monosaccharide transporters, such as GLUT1, GLUT4, or GLUT12, the main glucose transporters in breast cancer cells (Laudanski et al., 2004; Garrido et al., 2015; Matsui et al., 2017).

Bcl-2 family plays a role in mitochondrial-dependent apoptosis (Bata and Cosford, 2021; Changizi et al., 2021). The *Bcl-2/Bax* regulates apoptosis mediated by the mitochondrial pathway (Wang et al., 2016). Our results showed that the cell viability was significantly higher when exposed to a higher glucose concentration in conjunction with the increase of the *Bcl-2/Bax* ratio. Meanwhile, MCF7 cultured with fructose and combination media with higher fructose content had low *Bcl-2* and *Bax* mRNA expression. These results can be explained by a study in muscle cells showing that fructose exposure induced oxidative stress, triggered mitochondrial dysfunction, and disrupted the expression of *Bcl-2* family members and caspases (Jaiswal et al., 2015). Likewise, a study on Huh7 and A52 hepatocellular carcinoma cells showed that fructose promoted apoptosis, which was most likely caused by ROS accumulation and energy insufficiency (Dewdney et al., 2020). Further studies are needed to clarify whether this mechanism also applies to other cancer cells, including breast cancer cells.

In conclusion, this study added to the evidence that the higher the portion of glucose in the media, the greater the growth and migration ability of breast cancer cells. Meanwhile, fructose without the presence of glucose only slightly increased cancer cell viability, accompanied by suppressing *Bcl-2* expression. *GLUT5* was most likely the main transporter for glucose and fructose, and *GLUT7* was an alternative for fructose when these two hexoses were present together in the medium at a particular concentration. This research gave rise to unexpected results regarding the role of fructose in cell viability and growth and its capability to induce apoptosis of breast cancer cells. Therefore, further studies are needed to clarify the role of fructose, at what levels can this hexose alone support the growth and increase the progression of breast cancer cells or, conversely, have the potential to suppress the cells' growth.

Author Contribution Statement

The authors confirm contribution to the paper as follows: concept and design the experiments: HM, IY, and MH; performed experiments, data collection, prepared and visualized manuscript draft: HM, IY; supervised the study, discussed the design, results, and revised draft: IY, MH, RN, IA, and LH; performed data processing and interpretation of results: HM and HA. All authors reviewed the results and approved the final version of the manuscript.

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Approval

This study was approved by the Master Programme of Biomedical Sciences, Graduate School Universitas Hasanuddin, Makassar, Indonesia, as part of a student thesis (Harlindah Margawati), supervised by Dr. Ika Yustisia and Marhaen Hadjo, PhD.

Ethical Declaration

The present study was approved by the Health Research Ethics Commission Hasanuddin University with reference number 114/UN4.6.4.5.31/PP36/2023.

Conflict of Interest

The authors declare no conflict of interest.

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