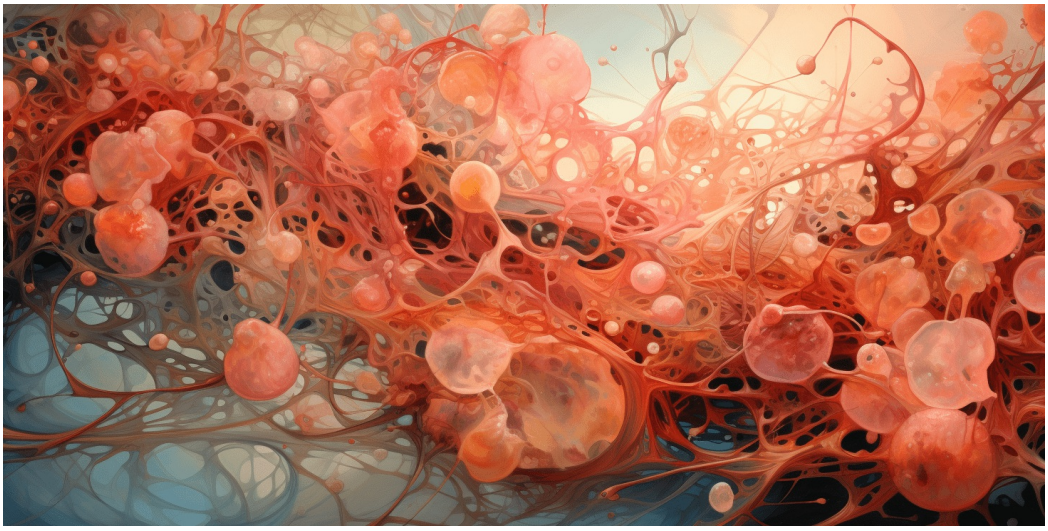

Developing the theory of Toxic Chemotherapeutic Nutrition for Cancer Cells: Glucosodiene Polymer Structure, Safety, Efficacy, and Human Outcomes in Targeting Tumors via Glucose Mutation

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Abstract

Cancer is a complex genetic disease characterized by aberrant cellular behaviors, including uncontrolled growth, invasion, and metastasis. The development of personalized treatment strategies based on genomic profiling has led to improved outcomes. Recent scientific endeavors have focused on targeting cancer through metabolic approaches, capitalizing on the altered metabolic pathways in cancer cells. Glucosodiene polymer, a newly derived compound from glucose, has shown promising results in inhibiting glucose metabolism and modifying the tumor's microenvironment acidity. The Maher Akl Theory of "Glucose Mutation" proposes a strategic approach to target cancerous tumors by inhibiting glucose metabolism and altering the tumor's microenvironment acidity using glucose isomer polymers. The goal is to disrupt the metabolic activity of the tumor and potentially modify and control the disease. This manuscript provides an overview of the metabolic vulnerabilities of cancer cells, evaluates the synthesis and chemical structure of glucosodiene, documents its safety, and explores its potential as a targeted therapy for cancer treatment. Additionally, a subset of successful clinical trials is presented, focusing on a case of successful treatment of triple-negative breast

cancer (TNBC) with glucosodiene. The potential mechanisms of action of glucosodiene in cancer, including its impact on glucose metabolism, modulation of signaling pathways, and immune-enhancing effects, are discussed.

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1. Introduction

Cancer is a complex disease that has undergone evolving definitions over time. Initially, it was characterized as uncontrolled cell growth and proliferation. [1] However, recent advancements in cancer research have led to a more nuanced understanding. Nowadays, cancer is recognized as a genetic disease resulting from cellular regulatory defects, encompassing a range of disorders characterized by abnormal cell behaviors, including uncontrolled growth, invasion, and metastasis. [2] This updated definition emphasizes the underlying genetic alterations and the diverse nature of cancer. The treatment of cancer involves various modalities, such as surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy. [3] Each modality aims to eradicate or control cancer cells through different mechanisms. Surgery involves the physical removal of tumors, while chemotherapy utilizes cytotoxic drugs to kill rapidly dividing cells. Radiation therapy employs high-energy radiation to damage cancer cells' DNA, impairing their ability to replicate. Immunotherapy harnesses the body's immune system to recognize and eliminate cancer cells, and targeted therapy focuses on specific molecular targets within cancer cells. [4] The efficacy of these treatment modalities varies depending on the cancer type, stage, and individual patient factors. Personalized treatment approaches based on genomic profiling are gaining prominence, allowing for tailored therapies with improved outcomes. [5]

Recent scientific endeavors have focused on targeting cancer through metabolic approaches. One hallmark of cancer cells is their heightened glucose consumption compared to normal cells. Cancer cells rely on altered metabolic pathways, including aerobic glycolysis, to meet their energy demands and promote tumor growth. [6] The metabolic alterations lead to the accumulation of lactate and a decrease in pH, resulting in an acidic tumor microenvironment. Researchers are exploring strategies to exploit these metabolic vulnerabilities, including inhibiting glucose metabolism, disrupting energy production, and altering the tumor microenvironment's acidity. [7] These metabolic approaches offer promising avenues for targeted cancer therapy. [8] The Maher Akl Theory of "Glucose Mutation", also known as "Toxic chemotherapeutic nutrition of cancer cells by alkaline glucosodiene molecules via targeting metabolic of cancerous tumors: a promising theory for cancer treatment," has been proposed as an innovative approach to target cancerous tumors, particularly those with solid or clustered growth patterns, by exploiting their metabolic activity.[9] This theory involves the synthesis of glucose isomer molecules into polymers called glucose isomer polymers. These polymers are specifically designed to hinder glucose metabolism within tumors by leveraging the alkaline properties of the glucose isomer polymer, thereby impeding tumor growth and modifying the tumor's hydrogen ion concentration. The ultimate goal of the Akl Theory is to disrupt the metabolic activity of the tumor, potentially leading to disease modification and control. [10][11]

2. Hypothesis

The heightened glucose consumption by cancer cells can be attributed to several mechanisms. Firstly, cancer cells often exhibit upregulated expression of glucose transporters, such as GLUT1, GLUT2, GLUT3 [Figure 1], and other variants, which facilitate increased glucose uptake into the tumor cells. [12] This heightened glucose uptake provides the necessary fuel for cancer cell growth and proliferation.

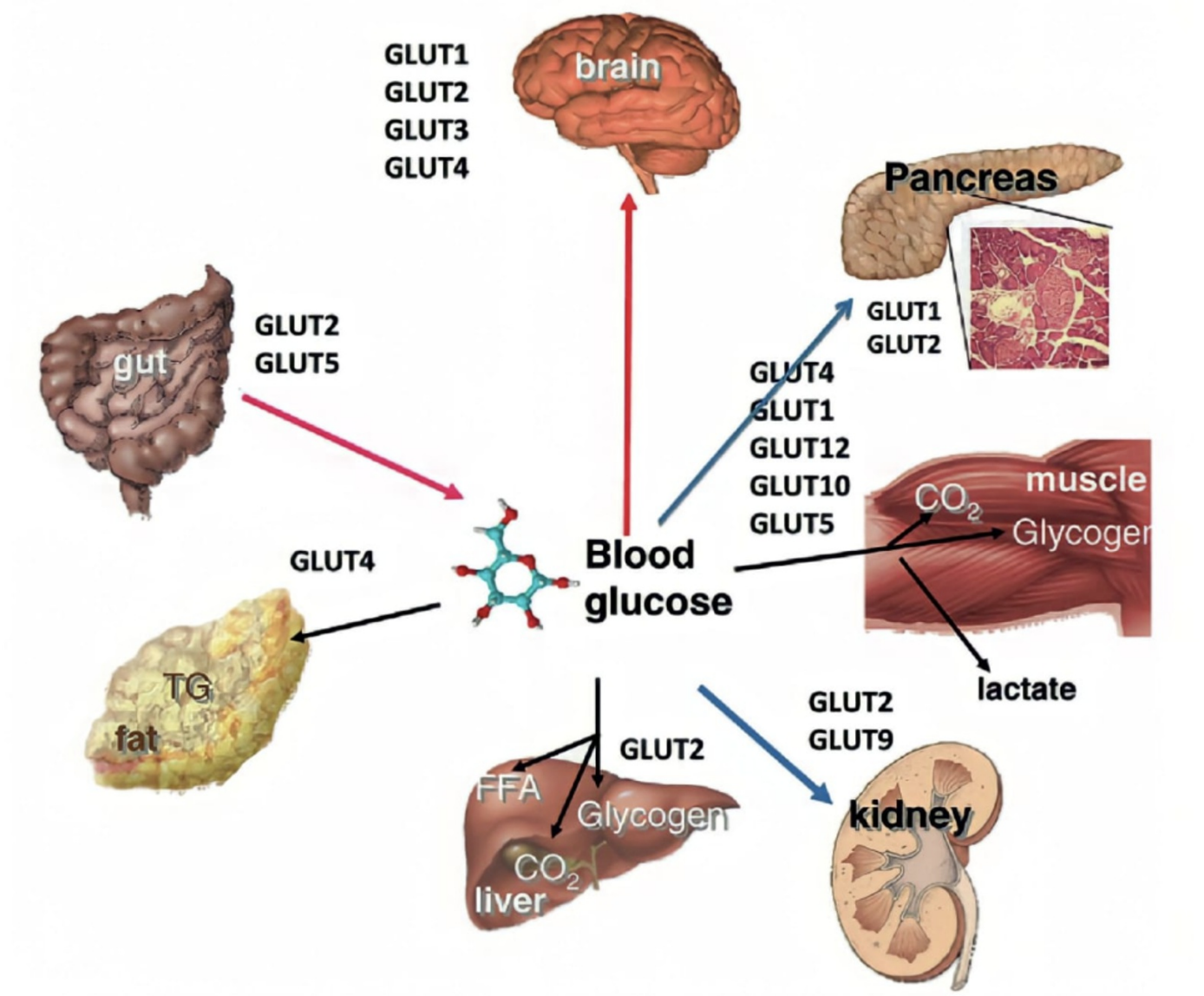

Figure 1. The role of GLUT proteins in maintaining glucose homeostasis is vital. These proteins facilitate glucose transport across cell membranes, ensuring glucose balance in the body. The diversity of glucose receptors in different organs underscores their significance in biological contexts. Consequently, alterations in these receptors may contribute to tumor development in affected organs. In the context of cancer cells, heightened glucose consumption can be attributed to mechanisms including upregulated expression of glucose transporters like GLUT1, GLUT2, and GLUT3.

As a consequence of this elevated glucose metabolism, cancer cells undergo glycolysis[Figure 2], a process that converts glucose into energy and produces large quantities of lactic acid. The accumulation of lactic acid results in the acidification of the tumor microenvironment. [13] This acidic environment plays a significant role in tumor progression and metastasis by promoting angiogenesis, immune evasion, [Figure 3] and tissue invasion. [14] By capitalizing on the reliance of cancer cells on glucose, a potential therapeutic strategy involves introducing a chemical alteration or structural mutation to the glucose molecule, allowing it to enter the tumor as a polymer with alkaline properties. This modified glucose polymer may hinder glucose metabolism within the tumor and alter its acidic hydrogen environment, thereby impeding tumor growth and spread, and potentially inducing cell death. Moreover, glucose serves as an attractive target for combating various types and stages of cancer since most cancerous tumors heavily rely on glucose metabolism, a phenomenon known as the

Warburg effect. [15] By targeting the metabolic activity of cancer cells and, specifically, their glucose receptors, it is possible to disrupt the tumor's nutrient supply and inhibit its growth. [16]

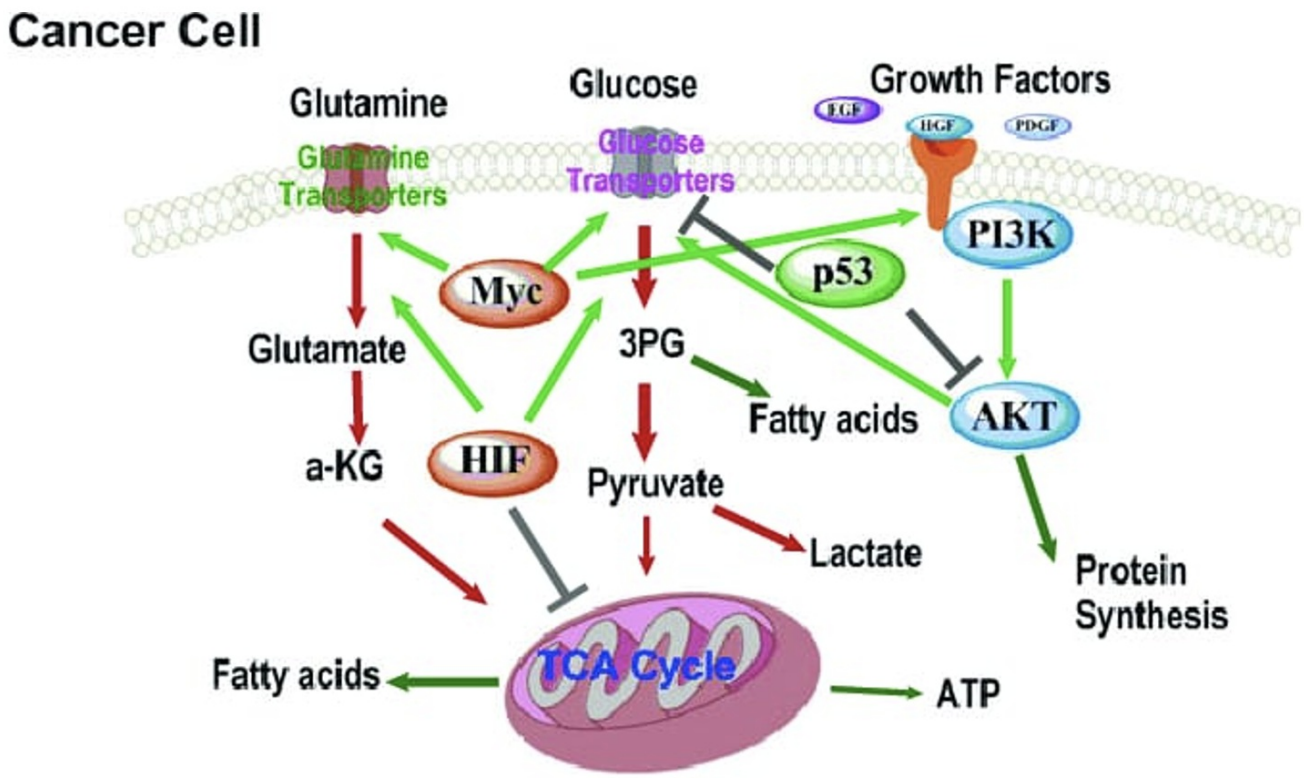

Figure 2. Cancer cells exhibit a metabolic shift called glycolysis, characterized by increased reliance on the conversion of glucose to lactate, even in the presence of oxygen (the Warburg effect). This metabolic adaptation provides cancer cells with the energy and building blocks required for their rapid proliferation. Glycolysis involves the enzymatic conversion of glucose to pyruvate, resulting in ATP production and the generation of NADH. The upregulation of glycolytic enzymes facilitates this process. Understanding glycolysis in cancer cells is essential for developing targeted therapies to disrupt their metabolic dependencies and inhibit tumor growth.

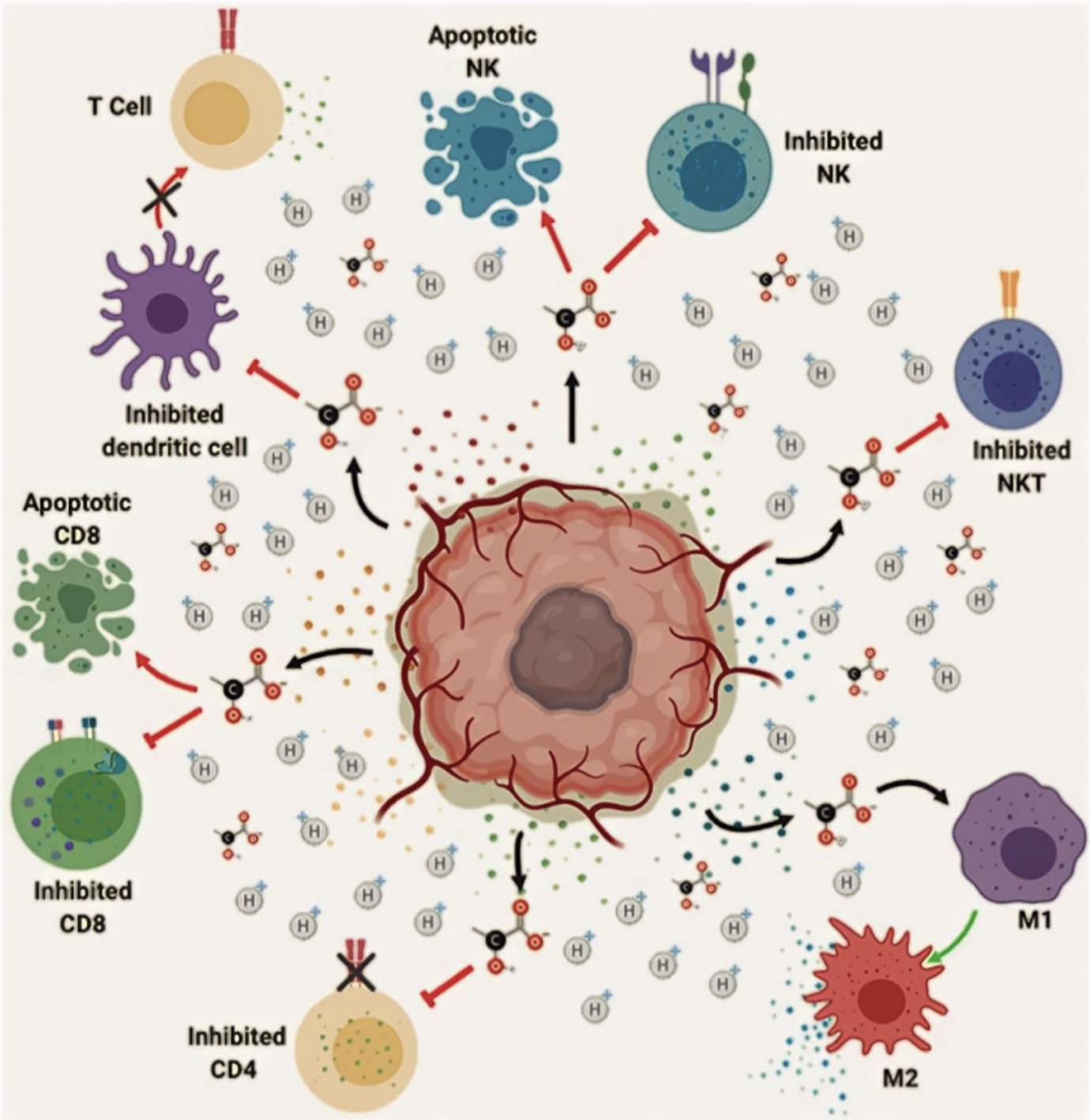

Figure 3. The acidic tumor microenvironment, facilitated by lactate secretion, plays a significant role in tumor progression and metastasis. It inhibits immune cell activation and proliferation, induces apoptosis in specific immune cells, and promotes the polarization of macrophages toward a pro-tumorigenic phenotype. This leads to immune suppression, immune evasion, and favorable conditions for tumor growth, invasion, and migration.

This can be accomplished by utilizing glucose as a carrier for delivering toxic substances directly to cancer cells or by inducing a structural mutation that imparts alkaline properties to glucose; understanding the metabolic characteristics of cancer cells and their dependence on glucose metabolism provides valuable insights for developing innovative therapeutic approaches aimed at targeting tumor cells through their metabolic vulnerabilities.

3. Methods

In this study, the synthesis of glucosodiene was carried out using dextrose monohydrate ($C_6H_{14}O_7$) and sodium bicarbonate ($NaHCO_3$) as the starting materials. The method employed involved the following steps. Weigh 3.5 grams of dextrose monohydrate and 2.5 grams of sodium bicarbonate accurately using a digital balance. Dissolve the measured quantities of dextrose monohydrate and sodium bicarbonate in 100 mL of sterile water. Stir the mixture gently to ensure uniform distribution. Heat the mixture to a temperature of 100 degrees Celsius using a heating apparatus. Maintain the mixture at this temperature for a duration of five minutes. Observe the reaction mixture closely for the formation of bubbles, which indicate the release of carbon dioxide. This confirms the occurrence of the reaction. Allow the reaction mixture to cool down to room temperature. Once the mixture has cooled, it can be subjected to further purification and characterization processes. It is important to note that the reaction between dextrose and sodium bicarbonate in this study was conducted under controlled conditions, including the use of sterile water and precise measurements of the starting materials. Heating the mixture to 100 degrees Celsius facilitated the reaction and allowed for the formation of glucosodiene. This method of synthesis follows established chemical principles and techniques. However, it is crucial to conduct further experiments and analyses to validate the purity, structure, and properties of the synthesized glucosodiene compound.

4. Glucosodiene

Glucosodiene is a novel compound synthesized through the reaction between dextrose and sodium bicarbonate. It is a polymer compound with a molecular formula of $C_{12}H_{22}O_{11}$. The synthesis of glucosodiene follows the scientific principle that elements with a common atomic structure, such as hydrogen and other first-row elements in the periodic table, share similar characteristics due to the presence of one electron in the valence shell. Glucosodiene is an isomer polymer of glucose and exhibits structural similarities to glucose. It is formed through the self-association of monomers derived from glucose isomers that are connected through 1-2 linkages. The molecular structure of glucosodiene is represented as (**1-2-O-β-D-Glucopyranosyl-α-D-glucose**). [Figure 4] The primary monomer responsible for the formation of the glucosodiene polymer is an isomer of glucose.

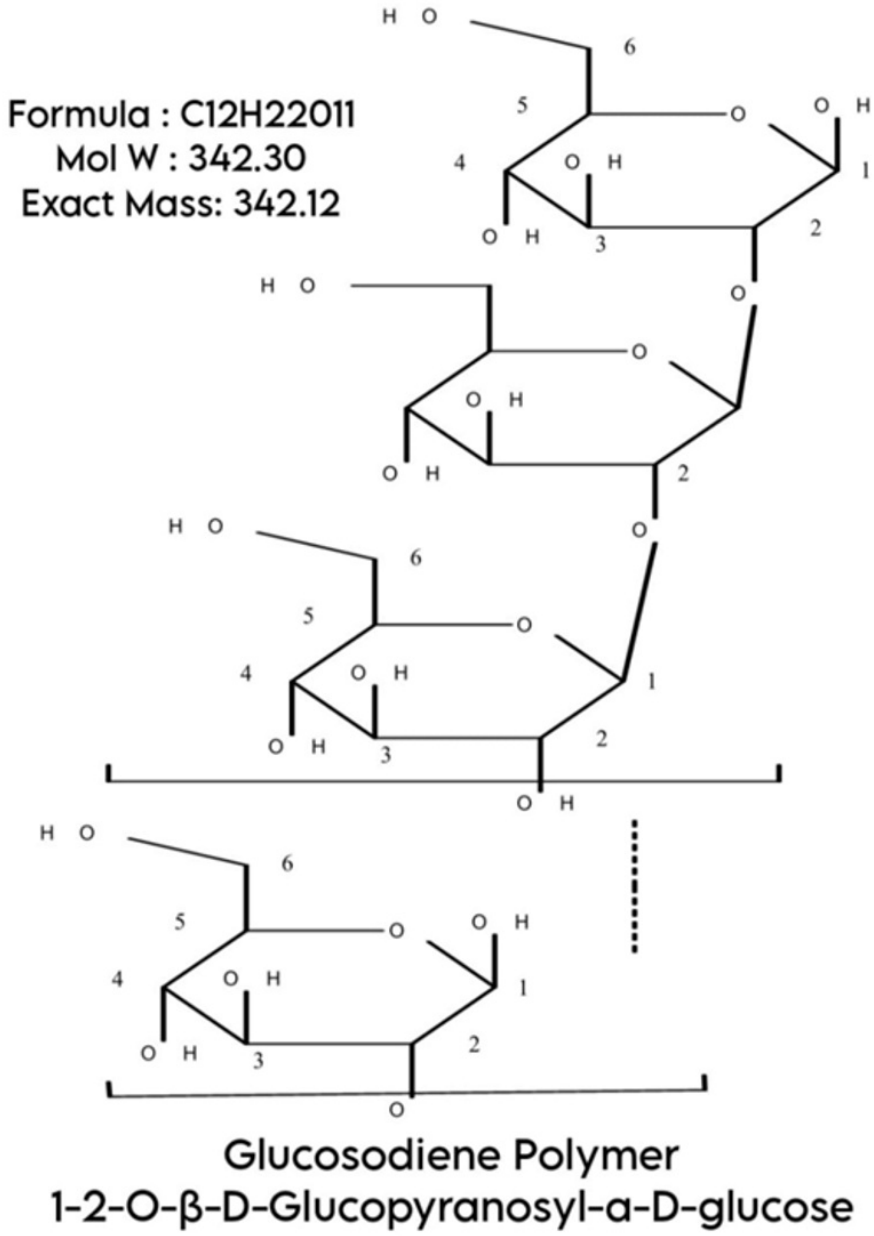

Figure 4. The structural configuration of the glucosodiene polymer is composed of monomers derived from glucose isomers that are connected through 1-2 linkages. Its molecular structure is represented as (**1-2-O-β-D-Glucopyranosyl-α-D-glucose**). The primary monomer responsible for the formation of the glucosodiene polymer is glucose, with a molecular mass of **178.9,** as determined by LC-MS results. Interestingly, this monomer shares a similar structural composition to trehalose but undergoes self-association through 1-2 linkages, resembling the molecular structure of sophorose.

The synthesis of glucosodiene involves the reaction between dextrose and sodium bicarbonate in a heated mixture. The resulting polymer compound is then dried and subjected to **NMR** [Figure 5, 6, 7] and

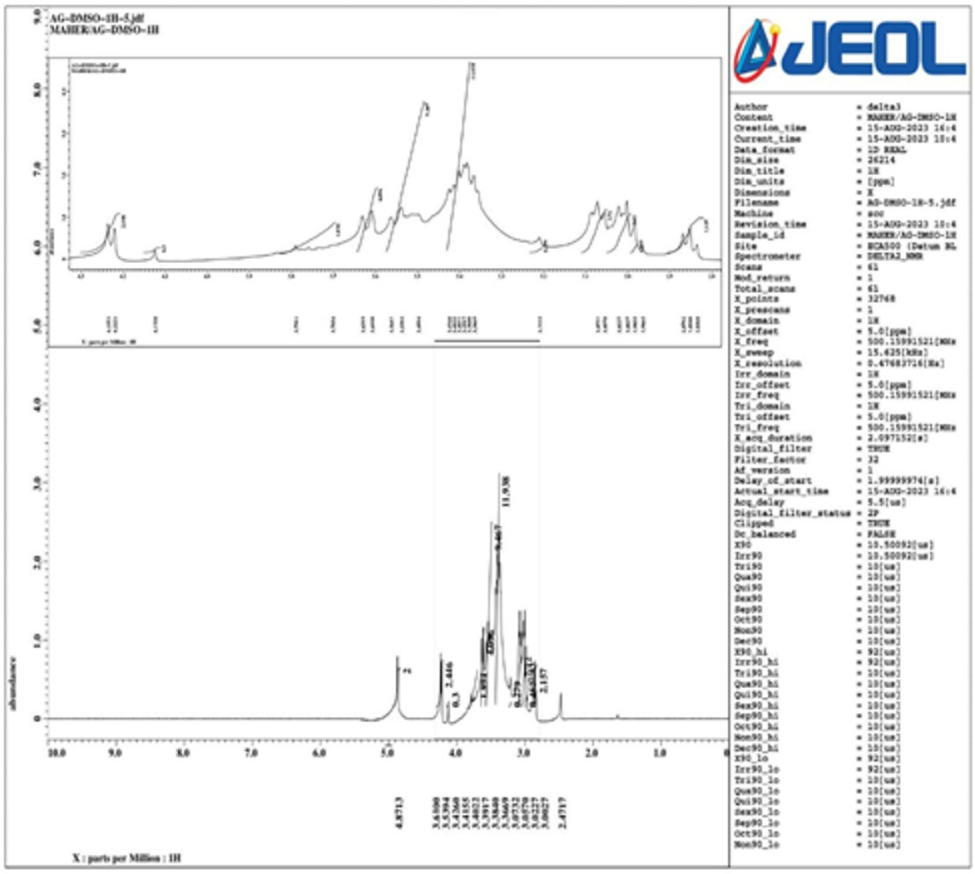

Figure 5. The NMR analysis of the synthesized compound showed the presence of C $_{12}H_{22}O_{11}$. Given the absence of aldehyde or ketone groups, the resulting compound can be identified as 1-2-O-β-D-Glucopyranosyl-α-D-glucose. The presence of $C_{12}H_{22}O_{11}$ confirms the formation of the desired compound.

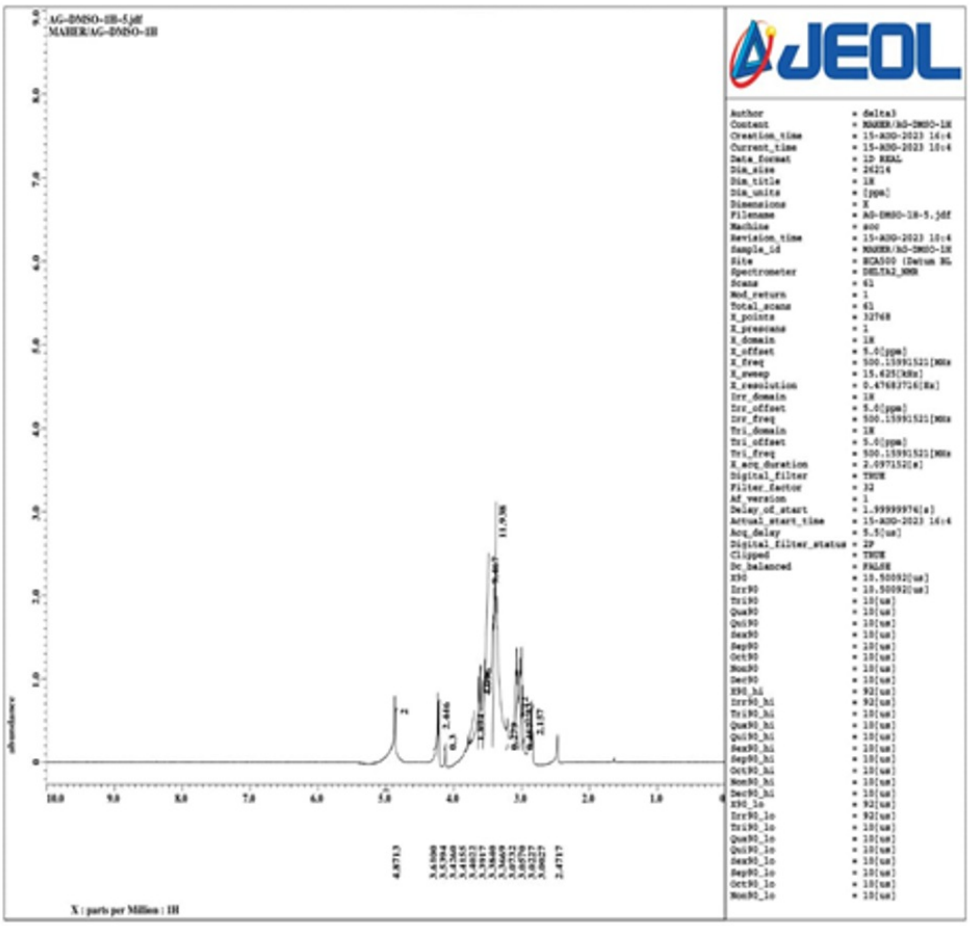

Figure 6. The NMR analysis of the synthesized compound showed the presence of C $_{12}H_{22}O_{11}$. Given the absence of aldehyde or ketone groups, the resulting compound can be identified as 1-2-O-β-D-Glucopyranosyl-α-D-glucose. The presence of $C_{12}H_{22}O_{11}$ confirms the formation of the desired compound.

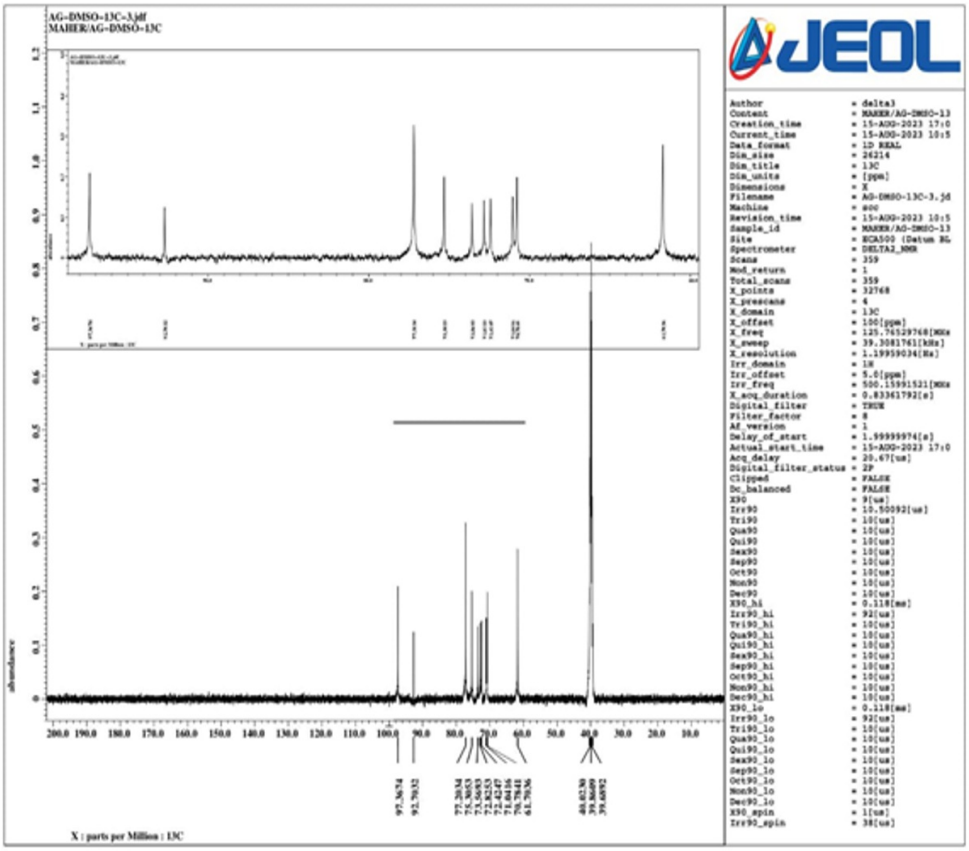

Figure 7. The NMR analysis of the synthesized compound showed the presence of C $_{12}H_{22}O_{11}$. Given the absence of aldehyde or ketone groups, the resulting compound can be identified as 1-2-O-β-D-Glucopyranosyl-α-D-glucose. The presence of $C_{12}H_{22}O_{11}$ confirms the formation of the desired compound.

LC-MS [Figure 8, 9, 10, 11] analysis. The NMR analysis confirms the presence of the formula $C_{12}H_{22}O_{11}$, while the LC-MS analysis validates its identity as 1-2-O-β-D-Glucopyranosyl-α-D-glucose.

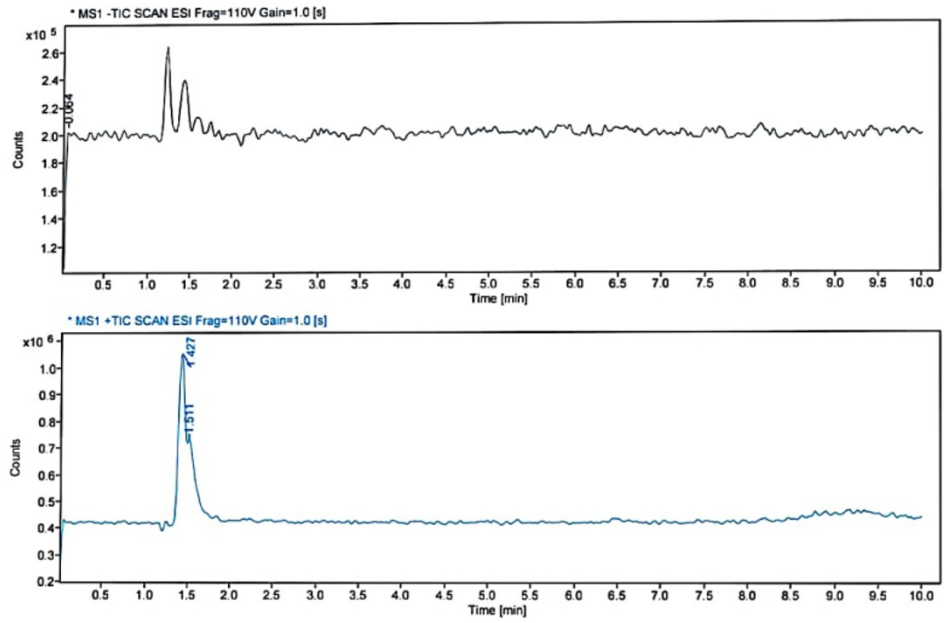

Figure 8. The molecular mass of the monomer was determined to be **178.9** based on the results obtained from LC-MS analysis. Interestingly, the monomer shares a similar structural arrangement to trehalose, but it undergoes self-association to form the polymer through 1-2 linkages, resembling the molecular structure of sophorose.

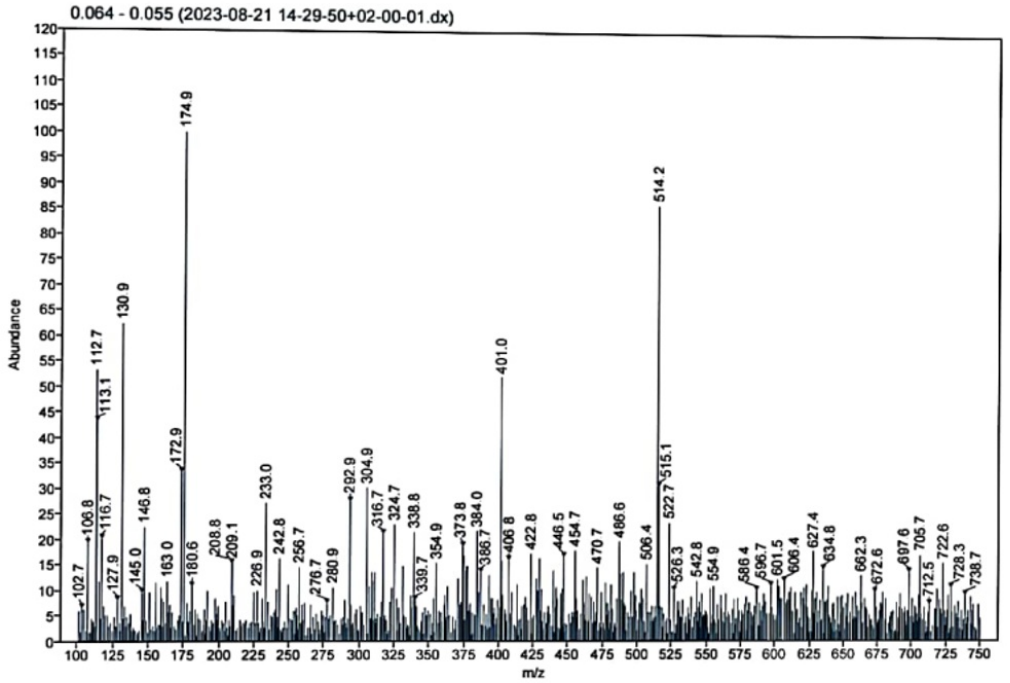

Figure 9. The molecular mass of the monomer was determined to be **178.9** based on the results obtained from LC-MS analysis. Interestingly, the monomer shares a similar structural arrangement to trehalose, but it undergoes self-association to form the polymer through 1-2 linkages, resembling the molecular structure of sophorose.

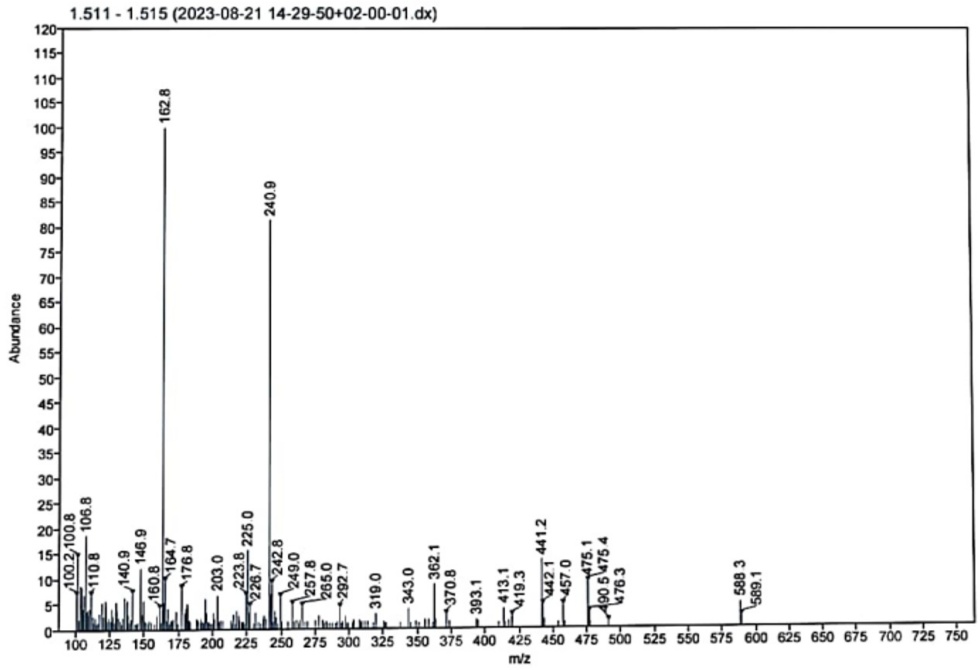

Figure 10. The molecular mass of the monomer was determined to be **178.9** based on the results obtained from LC-MS analysis. Interestingly, the monomer shares a similar structural arrangement to trehalose, but it undergoes self-association to form the polymer through 1-2 linkages, resembling the molecular structure of sophorose.

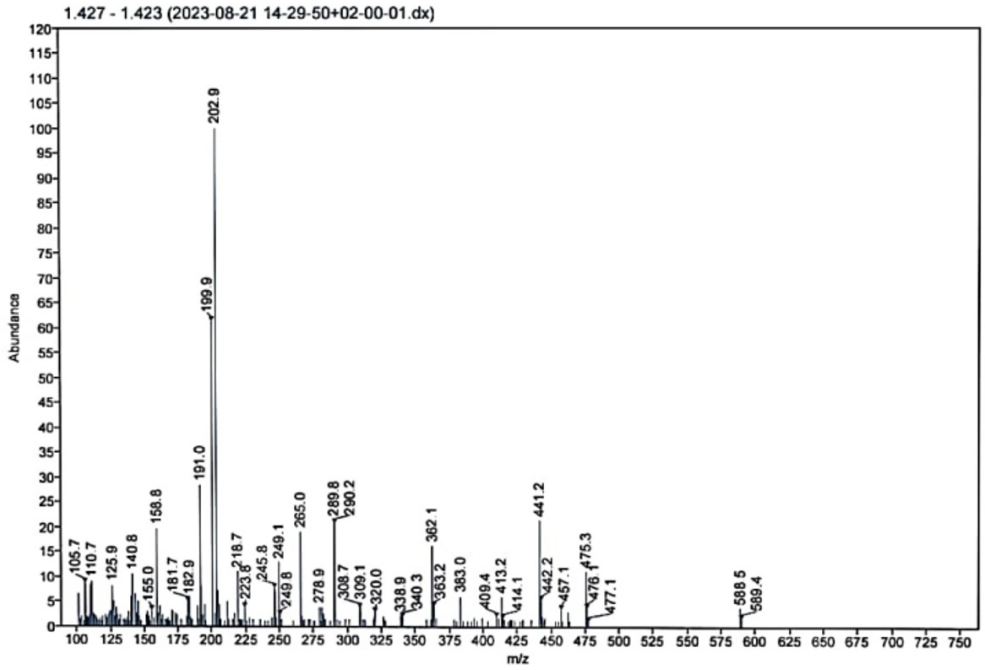

Figure 11. The molecular mass of the monomer was determined to be **178.9** based on the results obtained from LC-MS analysis. Interestingly, the monomer shares a similar structural arrangement to trehalose, but it undergoes self-association to form the polymer through 1-2 linkages, resembling the molecular structure of

sophorose.

5. The Safety of Glucosodiene on an In-Vitro Biopsy Cell Line Model

Cytotoxic effect on human normal fibroblast cell line (BJ1)

Remarks	LC_{90} (µg/ml)	LC_{50} (µg/ml)	Sample Code
0.3% at 100ppm	--------	--------	glucosodiene molecules
1% at 100ppm	--------	--------	DMSO
0 %	--------	--------	Negative control

The laboratory experiment was conducted to evaluate the safety of Glucosodiene using an in-vitro biopsy cell line model. The BJ1 normal skin fibroblast cells were utilized for this study. First, the cells were suspended in a DMEM-F12 medium supplemented with a 1% antibiotic-antimycotic mixture and 1% L-glutamine. The cells were then batch-cultured for 10 days. Afterward, the cells were seeded at a concentration of 10x103 cells/well in 96-well microtiter plastic plates and incubated for 24 hours at 37 ºC under 5% CO2. To assess cell viability, the mitochondrial-dependent reduction of yellow MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) to purple formazan was measured. The following steps were carried out in a sterile environment using a Laminar flow cabinet biosafety class II level. The cells were incubated either alone (negative control) or with different concentrations of Glucosodiene samples to achieve final concentrations of 100, 50, 25, 12.5, 6.25, 3.125, 0.78, and 1.56 ug/ml. After 48 hours of incubation, the medium was aspirated, and MTT salt (2.5µg/ml) was added to each well. The plates were further incubated for four hours at 37ºC under 5% CO2. To stop the reaction and dissolve the formed crystals, 10% Sodium dodecyl sulphate (SDS) in deionized water was added to each well and incubated overnight at 37ºC. The absorbance was measured at 595nm using a microplate multi-well reader with a reference wavelength of 620nm.

The percentage of change in viability was calculated using the formula: ((Reading of extract / Reading of negative control) -1) x 100). A probit analysis was conducted using the SPSS 11 program to determine IC50 and IC90 values. The results of the experiment demonstrated that Glucosodiene exhibited no cellular toxicity or adverse effects on the BJ1 normal skin fibroblast cells at a concentration of 100 ppm [Figure 12,13]. This suggests the safety of Glucosodiene on normal cells in the in-vitro model. [17][18]

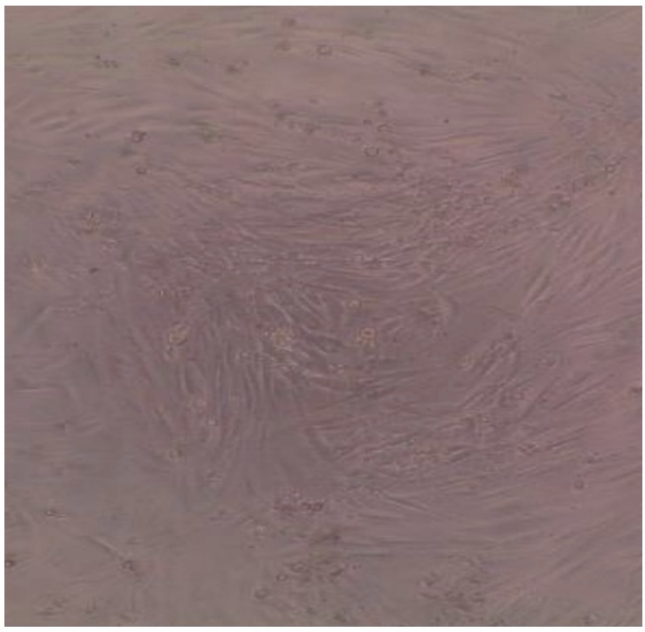

Figure 12

A Control

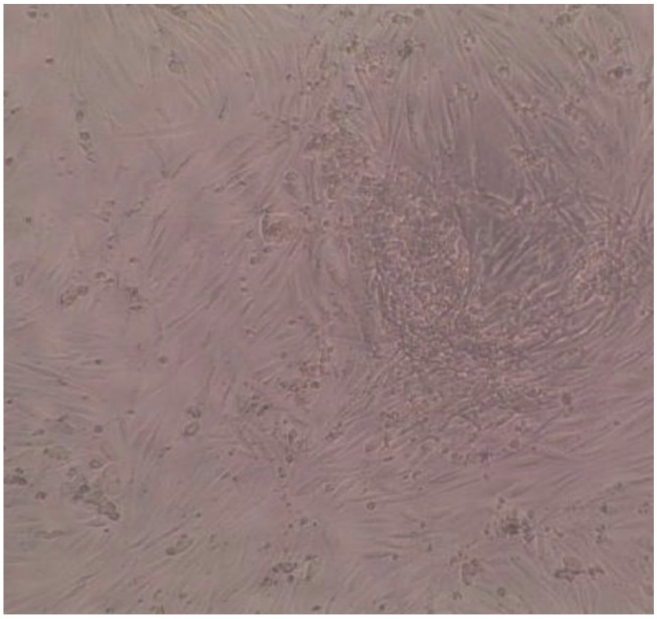

Figure 13

B Glucosodiene

Figures 12, 13. The results of the experiment demonstrated that Glucosodiene exhibited no cellular toxicity or adverse effects on the BJ1 normal skin fibroblast cells at a concentration of 100 ppm.

6. Successful First Case Treatment for Metastatic Triple Negative Breast Cancer (TNBC) of Bone by Glucosodiene

This manuscript presents the successful treatment of the first documented case of metastatic triple-negative breast cancer (TNBC) in the bones using glucosodiene. TNBC is an aggressive subtype of breast cancer that lacks estrogen receptors, progesterone receptors, and HER2. Glucosodiene is an alkaline glucose isomer that inhibits glucose metabolism within tumors, targeting the Warburg effect. The case report features a 42-year-old female patient with TNBC who had previously undergone unsuccessful traditional chemotherapy and presented with bone metastasis. Following 15 days of glucosodiene treatment [Figure 14, 15], the patient exhibited normal vital functions and no signs of cellular activity[14][15]. The promising results suggest the potential of glucosodiene as an effective treatment for advanced-stage TNBC in a clinicaltrials.gov number (**NCT05957939**).

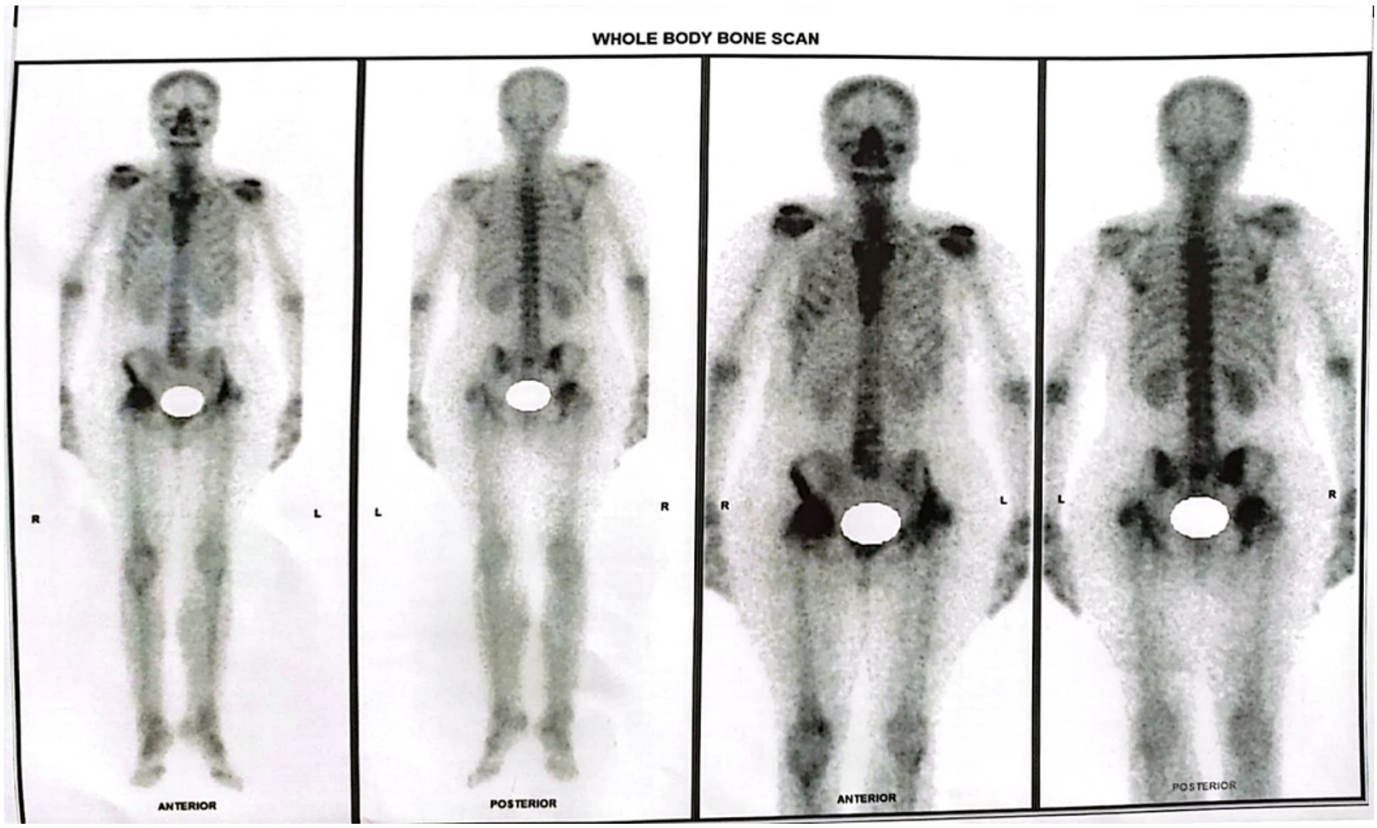

Figure 14. This is the scanned image of the patient prior to treatment or the latest bone scan before the decision to treat with glucosodiene. **The publication of this image has been approved by the patient and the owner of this clinical study following its initial publication in the pre-print version.** The patient presented with right leg pain, which prompted a bone scan revealing osseous metastasis in multiple locations, including the right iliac bone, head and trochanteric area of the right femur, right ischium, left acetabulum, and trochanteric area of the left femur.

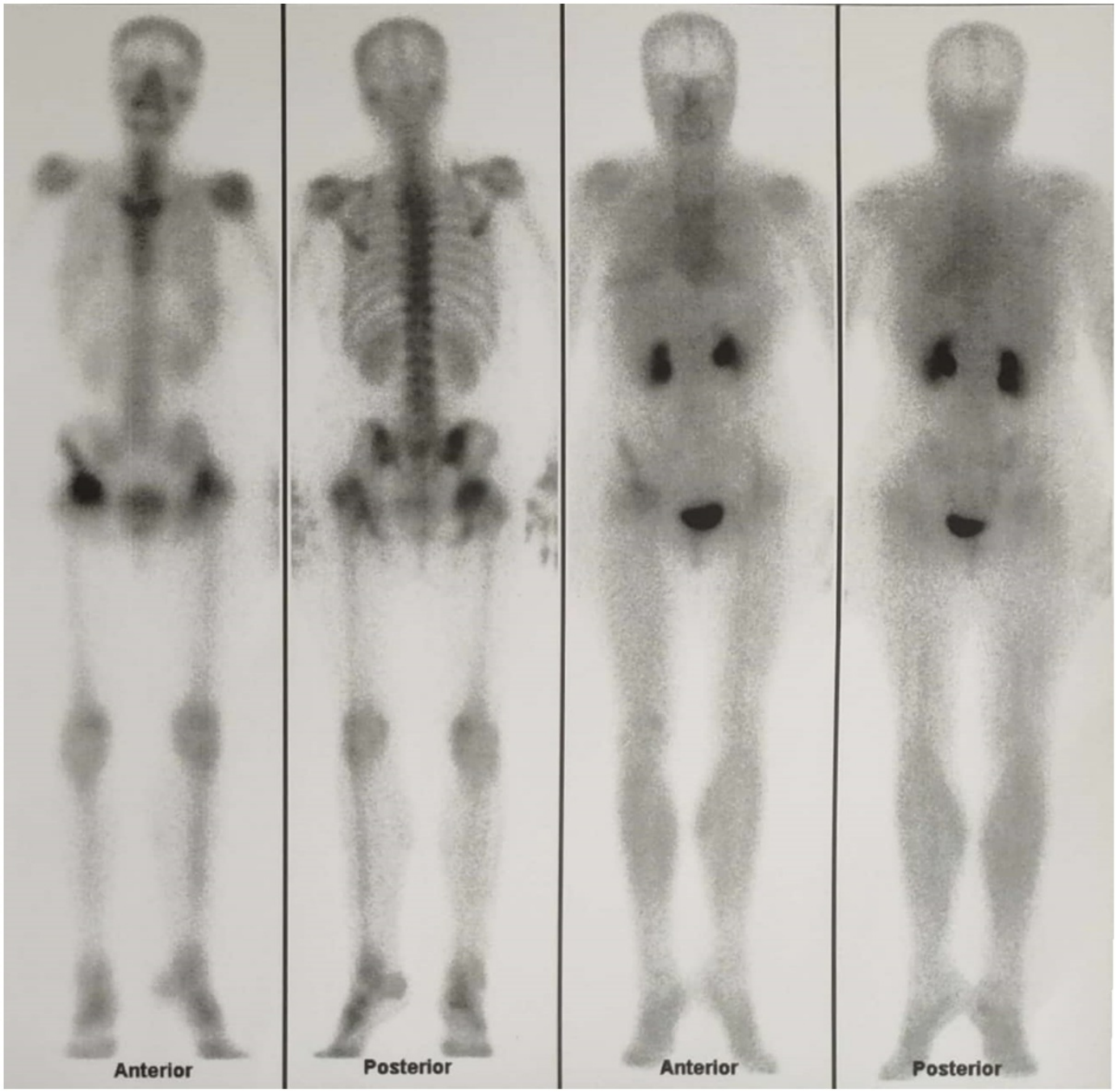

Figure 15. This is an atomic scan image of the patient after treatment or with glucosodiene. **The publication of this image has been approved by the patient and the owner of this clinical study, after it was initially published in its pre-print version**. An isotopic bone scan using dual-phase bone scintigraphy revealed consistent uptake of the tracer in the previously identified regions, accompanied by slight hyperemic changes during the blood pool phase. The remaining skeletal areas exhibited uniform distribution of the tracer, without any active or cold focal lesions.

7. Potential Mechanisms of Action of Glucosodiene Polymer in Cancer

The compound Glucosodiene Polymer 1-2-O-β-D-Glucopyranosyl-α-D-glucose has been identified for its important anticancer properties, although the precise mechanisms of its action remain unclear. However, we are attempting to explore the potential mechanisms through which Glucosodiene Polymer exerts its anticancer effects. One of the expected fundamental mechanisms of action of Glucosodiene Polymer is its ability to inhibit enhanced glucose metabolism

observed in cancer cells.

Glucose metabolism is vital for the rapid growth and proliferation of cancer cells. By disrupting this metabolic pathway, Glucosodiene Polymer impairs the production of energy and essential biological processes necessary for the survival of cancer cells. As a result, cellular ATP levels decrease, affecting various cellular functions and ultimately hindering tumor growth. In addition to its impact on glucose metabolism, Glucosodiene Polymer is expected to modulate signaling pathways involved in the survival and proliferation of cancer cells. Specifically, it may inhibit the activation of crucial protein kinases, including Akt and ERK, which play critical roles in the survival and growth of cancer cells. Interfering with these signaling pathways may result in cell cycle arrest and stimulate programmed cell death, known as apoptosis, in cancer cells. Furthermore, Glucosodiene Polymer may exhibit immune-enhancing effects that promote an immune response against cancer. This can be achieved through cytokine production and activation of immune cells such as stem cells and effector cells.

Through its immune activity, Glucosodiene Polymer is likely to contribute to tumor suppression and enhance anti-tumor immune response. These findings have been inferred from observations and results recorded in a clinicaltrials.gov number (**NCT05957939**) involving the treatment of triple-negative breast cancer with bone metastasis using glucosodiene.

8. Discussion

Cancer cells exhibit an increase in glucose uptake through the upregulation of glucose transporters, which fuels their rapid growth and proliferation. Maybe Glucosodiene works by inhibiting glucose metabolism within tumors, impairing energy production, and altering the tumor's microenvironment acidity. This disruption impedes tumor growth and spread, potentially leading to cell death. Maybe Glucosodiene also regulates signaling pathways involved in the survival and spread of cancer cells, inhibiting crucial protein kinases and promoting cell cycle arrest and programmed cell death. Additionally, it may enhance the anti-tumor immune response by stimulating cytokine production and activating immune cells. The successful treatment of triple-negative breast cancer (TNBC) in bones using glucosodiene highlights its potential as an effective therapy for advanced-stage cancer. A case report demonstrates the ability of glucosodiene to inhibit cellular activity and underscores its clinical significance in targeting cancer metabolism.

9. Conclusion

Glucosodiene, also known as the "glucose mutation," holds great promise as a therapeutic strategy for cancer treatment. It exhibits inhibitory effects on glucose metabolism, modulates signaling pathways, and possesses immune-enhancing properties, making it an attractive candidate in the fight against cancer. However, further research is necessary to fully comprehend the underlying mechanisms of action and optimize the therapeutic potential of glucosodiene. With ongoing investigations, glucosodiene has the potential to revolutionize cancer treatment by exploiting the metabolic vulnerabilities

of cancer cells and offering personalized and effective treatment options.

Statements and Declarations

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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