International Journal of Multidisciplinary and Current Research ISSN: 2321-3124
Review Article Available at: http://ijmcr.com

Glucose Analogue (2-DG): A Novel Therapy for Covid 19

Athira Roy[1], Krishnaveni K[1]*, Sambathkumar R[2]

[1] Post Graduate Student, [1*] Associate Professor, Department of Pharmacy Practice [2] Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Namakkal (Dt), Kumarapalayam- 638 183, Tamil Nadu, India.

Received 10 Sept 2021, Accepted 01 Oct 2021, Available online 05 Oct 2021, **Vol.9 (Sept/Oct 2021 issue)**

Abstract

In India, 2-Deoxy-D-Glucose (2-DG) has been licenced for the treatment of active corona patients with moderate to severe symptoms. This novel glucose analogue could destroy cancer cells synergistically when combined with other effective cytotoxic drugs. Glucose provides energy to all of the cells in the human body. 2-DG inhibits glycolysis and ATP production by acting as an anti-glycolytic agent. Consumption of 2-DG creates starvation in high-glucose-using cells, which leads to autophagy. The similar anti-glycolytic property has led to its inclusion in a number of clinical trials to investigate its blocking mechanism in the pathogenesis of SARS Corona Virus-2 (SARS-CoV-2). According to the trials, the drug can cause viral death and lessen oxygen dependency in active corona patients. However, the impact of 2-DG on healthy cells such as neurons is also a source of worry. The study collectively investigates into the anticancer, antiviral, and biological properties of 2-DG.

Keywords: *COVID-19, 2-Deoxy-D-Glucose, SARS-CoV-2, Cancer.*

Introduction

Since 2019, the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has become one of the most serious health crises.[1] It has now evolved into a widespread and deadly pandemics of the twenty-first century. In the month of December 2019, the first case of COVID-19 was discovered in Wuhan, China. It has since expanded to over 220 nations throughout the world. With over 24 million cases and 338,000 deaths as of April 2021, India is now the epicenter of the global pandemic, with more than 24 million cases and 338,000 deaths. As the global number of infections rises, research and drug approvals are accelerated in order to find a definitive cure for the disease. Various preemptive efforts have been implemented around the world to control the disease's wandering spread. However, presently there is no recognized treatment for COVID-19. SARS-CoV-2 virus replication has recently been demonstrated to be inhibited by 2-deoxyglucose/ 2 -deoxy-D-glucose (2-DG). The Drug Controller General of India (DCGI) has approved the emergency use of 2-DG as an adjunct therapy for moderately and severely infected corona patients, which is a ray of hope in the fight against COVID-19. Defense Research and Development Organization (DRDO) and Dr. Reddy's Laboratories (DRL) collaborated on the medicine, which was authorized on May 8, 2021.

*Corresponding author's ORCID ID: 0000-0003-0161-3194
DOI: https://doi.org/10.14741/ijmcr.v.9.5.3

2-DG is a glucose analogue. The initial research into the use of 2-DG for cancer treatment shed light on how the drug works, revealing that it competes with glucose metabolism in cancer cells, depleting cancer cells of the energy they require to survive and multiply, ultimately causing malignant tumour cells to die.[2] The discovery that 2-DG inhibits glycolysis by forming and accumulating 2-deoxy-D-glucose-6-phosphate (2-DG6P), blocking hexokinase and glucose-6-phosphate isomerase, and triggering malignant cell death, led to its potential therapeutic use in the treatment of COVID-19.[3] It further stated that, due to its basic composition, it can be easily produced and made available in large quantities throughout the country, generating expectations that it may someday be extensively used and help to alleviate the current COVID crisis. Due to its method of action in infected cells, the medicine is likely to save precious lives in a huge number of patients who are suffering from severe oxygen dependency and require hospitalisation. Some detractors, however, argue that there is insufficient evidence to support the drug's emergency approval as a COVID-19 treatment.

2-DG and how does it work

It's glucose analogues, which have the appearance of glucose but aren't. When comparing the structures of glucose and 2-DG, the second carbon in 2-DG varies from glucose (Figure 1 Structural representation of 2-DG and

Glucose). To prevent glycolisation, the second carbon in glucose's hydroxyl group is substituted with a hydrogen atom in 2-DG.[4] 2-DG has been tested for its ability to target cancer cells all over the world. By blocking glycolsis, it has the ability to cause cell death.[5] A fast-multiplying microbe in the human body requires glucose for energy. As a result, the virus will consume this glucose analogue, disrupting glucose metabolism and protein glycosylation even more. As a result, the medicine will stop microorganisms from multiplying.[3] According to a study published in 2010, cancer can cells ingest 2-DG at a higher rate than normal cells, hence it can be utilised as a cancer cell marker.[6] To increase its anti-glycolytic effect, the hydrogen atom at the second position of 2-DG can be substituted with a fluorine atom.[7] By putting glycolysis as a crucial upstream process during SARS-CoV-2 pathogenesis, 2-DG, as an anti-glycolytic drug, plays a key role in preventing viral multiplication and cytokine response.[8] Now that India has approved the use of 2-DG for COVID-19 in an emergency situation, the medicine will be available in sachets containing powder that can be dissolved in water.

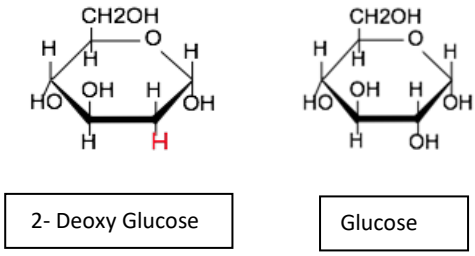

Figure 1: Structural representation 2-DG and glucose

2-DG is an experimental medication that is being researched as an anticancer and antiviral treatment. The melting point of 2DG is 142-144°C. 2-DG interacts with various cellular pathways and has a variety of physiological effects such as Autophagy Induction, Apoptosis Induction, Protein N-Glycosylation, and so on, rather than simply acting as a glycolysis blockage.

Biological activity of 2-DG

Glycolysis Inhibition

2-DG competes with glucose for transfer into the cell and can impede glucose transport. In cancer cells, oxygen shortage, which is more common in the intratumoral environment, increases the expression of glucose transporters and glycolytic enzymes, which increases 2-DG uptake compared to normal cells in an aerobic environment.[7] Hexokinase II phosphorylates 2-DG to 2-deoxy-d-glucose-6-phosphate when it enters the cell (2-DG-6-P). This results in the accumulation of 2-DG-6-P within the cell, as well as allosteric and competitive inhibition of hexokinase isomerise, which leads to Adenosine Triphosphate (ATP) depletion, cell cycle arrest, inhibition of cell growth, and eventually cell death. As a result, the bigger the accumulation of 2-DG-6-P, the greater the impact on glycolysis.[9] Because cancer cells can continue to make ATP utilising alternate sources, such as fatty acids or amino acids, inhibition of glycolysis is more effective under hypoxic settings.[10]

Autophagy Induction

Glycolysis inhibition causes ATP deficit, which changes the ATP/ Adenosine Monophosphate (AMP) ratio and activates AMP-activated protein kinase (AMPK).[11] Active AMPK phosphorylates the proteins in the Mammalian Target of Rapamycin (mTOR) kinase complex, causing autophagy to be induced.[12] Autophagy is a destructive process that occurs in all living cells. Autophagy is the process of encapsulating intracellular organisms in double-membraned vesicles called autophagosomes and transporting them to lysosomes for destruction.[13] Autophagy promotes tumour development in the early stages of growth, boosts cancer cell survival and promotes metastasis in advanced tumours.[14] AMPK activation may also cause p53, a tumour suppressor protein, to be expressed. The cell cycle is arrested at the G1 checkpoint by active p53, which then targets the cell for apoptosis.[15] Sugars, nucleosides or nucleotides, amino acids, and fatty acids, among other breakdown products of autophagosomal cargo, can be carried back to the cytoplasm, presumably to re-enter cellular metabolism. Sustained autophagic flow, on the other hand, may result in excessive self-degradation of vital cellular components (such as mitochondria) which in turn can trigger cell death.

Apoptosis Induction

Apoptotic cell death is the result of prolonged autophagy and significant self-degradation. Depending on the cell type, powerful 2-DG apoptotic induction appears to be communicated via distinct routes. ATP depletion sensitises cells to Tumor Necrotic Factor (TNF) leading to receptor dependent extrinsic apoptosis, according to study conducted by *Munoz-Pinedo, et al.,* [2003] [16] through cytoprotective autophagy processes, *Xu, et al.,* in 2005 [17] discovered that 2-DG can sensitise cells to apoptosis. Furthermore, 2-DG has been shown in multiple studies to increase Reactive Oxygen Species (ROS) production, resulting in cell death.[18] *Valera, et al.,* in 2017 discovered that 2-DG treatment alters the B-cell lymphoma 2 (Bcl-2) / Bcl-2 Associated X (BAX) apoptosis regulator protein ratio in bladder cancer cells, driving apoptosis induction.[19]

Protein N-Glycosylation

Many secreted or membrane-bound glycoproteins contain N-glycans, which are involved in a variety of critical processes such as protein stability, folding,

intracellular interactions, and signal transmission. They also play a role in cell–cell and cell–extracellular matrix interactions as well as cell adhesion mediation.[20] The common core pentasaccharide, which consists of three d-mannose and two -d-N-acetylglucosamine (GlcNAc) molecules, is found in all eukaryotic N-linked glycans. The glycan glucose3-mannose9-N-acetylglucosamine2 (G3Man9GlcNAc2) is transferred from a lipid-linked oligosaccharide (LLO) by a co translational process, resulting in the three primary forms of glycans: high-mannose, hybrid, and complex N-glycans.[21] When LLO synthesis is disrupted, abnormal N-linked glycosylation occurs, interfering with the Erthroplasmic Reticulum's glycan-dependent folding and quality control activities (ER).[22] D-mannose and d-glucose are quite similar, with the exception of the stereochemistry at the C-2 position. The hydroxyl group at C-2 was removed from d-glucose to produce 2-DG. The identical 2-DG product results by removing the hydroxyl group at C-2 in the d-mannose molecule. Thus, 2-DG can disrupt d-glucose and d-mannose metabolism by suppressing glycolysis, altering mannose-related metabolic pathways, and competing with d-mannose for protein N-glycosylation.[23]

2-DG and Covid

The DCGI has issued emergency approval to 2-DG, an oral antiviral formulation. The medication comes in a sachet (2.43 gm) and is administered orally at 45mg/kg twice a day before meals by dissolving it in water. Its anti-COVID-19 therapeutic application has been developed by the Institute of Nuclear Medicine and Allied Sciences (INMAS), a laboratory of the DRDO, in cooperation with DRL, Hyderabad.

2-DG can only be given to hospitalised moderate-to-severe COVID-19 patients on prescription as an adjunct (add-on) therapy to the existing standard of care (SOC). The composition, according to the manufacturers, aids in the speedier recovery of COVID-19 patients in hospitals and minimises their reliance on supplementary oxygen. 2-DG can be easily made and provided in big quantities because it is a generic chemical and a glucose analogue.

How does the formulation work?

In virus-infected human cells, the main function of the 2-DG medication is to suppress glycolysis (the breakdown of glucose by cells for energy). Viruses rely on glycolysis to meet their energy needs. The energy provided by glycolysis aids the virus's reproduction in the human body. By selectively accumulating in virus-infected cells, the 2-DG drug suppresses glycolysis. The 2-DG medication prevents viral replication in human cells by decreasing glycolysis. According to a study conducted by *Griffin TJ, et al.,* in 2002, 2-DG possesses antifungal activity against Saccharomyces cerevisiae.[24] To sustain optimal cell growth and survival, cells have the ability to adapt to changes in nutrition supply. Even when glucose is available, adding 2-DG to the cells triggers a glucose-starvation-like reaction in the cells, which limits growth and reduces viability.[25] 2-DG suppresses cell-wall polysaccharide biosynthesis and glycoprotein biosynthesis, according to a study published in 1982.[26] According to a study published in the year 2020, 2-DG has improved viral penetration against the herpes simplex virus.[27] When treated with 2-DG, the production of infectious herpes simplex virus was reduced by 94-98 percent (%). In a 2020 experiment involving chick embryo and yeast cells, 2-DG was found to have antiviral properties by preventing the glycosylation of viral glycoproteins. According to the findings of a study, 2-DG inhibits glucose flow whereas oligomycin inhibits ATP synthase.[28] In the same investigation, 2- DG was found to be safe in the treatment of SARS-CoV-2. It totally inhibits viral replication in CoV-2-infected monocytes, as well as the CoV-2-induced upregulation of Angiotensin-converting Enzyme 2 (ACE2). Another study published in 2021 found that 2- DG inhibits SARS-CoV-2 replication in a colon epithelial cancer cell line.[29] During SARS-CoV-2 pathogenesis, 2-DG inhibits viral replication and cytokine storm by compromising high energy demand and reducing glycolysis, according to this study. Another study published in 2020 by *Balakrisna, et al.,* recommends using 2-DG in combination with low-dose radiation treatment to protect SARS-CoV-2 sensitive tissues and organs and minimise COVID-19-related mortality and morbidity.[30] A analogue of 2-DG, 2-FluroDeoxy-D-Glucose (2-FDG), can be employed as a radiotracer in the detection of COVID-19 pneumonia, reducing the radiation exposure risk of Computed tomography (CT) scan that is said to be equivalent to 300 X-rays.[31]

Clinical trials

In April 2020, researchers from INMAS and the Centre for Cellular and Molecular Biology (CCMB) in Hyderabad revealed that the chemical 2-DG is efficient against the SARS-CoV-2 virus and inhibits viral proliferation in lab trials. The DCGI's Central Drugs Standard Control Organization (CDSCO) approved phase II clinical trials to investigate the 2-DG drug's safety and efficacy in COVID-19 patients in May 2020.

DRDO and DRL conducted phase II trials on 110 patients between May and October 2020. The phase II-a studies took place in six hospitals, whereas the phase II-b (dose-ranging) trials took place in eleven hospitals across India. In November 2020, the DCGI approved phase III clinical trials after reviewing the findings from phase II trials. 220 patients were included in the late-stage phase III trials, which took place in 27 COVID-19 facilities across ten states.

What does the trial data say?

The data from phase II trials found the drug to be safe in COVID-19 patients. Researchers noted that the COVID-19

patients treated with 2-DG demonstrated faster recovery than the SOC on various endpoints. On average, patients treated with 2-DG achieved normalization of specific vital signs parameters 2.5 days earlier than those treated only with SOC.

Similarly, the phase III clinical trial data showed that a significantly higher proportion of those who received 2-DG became free from supplemental oxygen dependence by Day 3 in comparison to those treated with SOC thereby, indicating an early relief from oxygen therapy. A similar trend was observed in patients aged 65 and above. According to the trial data, 2-DG was given 45 mg per kg of body weight in the morning and 18 mg per kg in the evening during its phase 2 study. This was increased to 45 mg/kg in the morning and 45 mg/kg in the evening in phase 3, for a total of 90 mg/kg per day. Based on the result of Phase II and phase III trials, 2-DG has received emergency use authorisation to be used as an adjunct therapy in moderate to severe COVID-19 patients in a hospital settings. But still evidences are lacking regarding its safety and efficacy, so more trials are indeed needed to assess its overall activity.[32]

Mechanism of action in cancer

Although the mechanism of 2-DG's action on cancer cells is not entirely understood, it is thought to be connected to glycolysis suppression. Inhibition of lipolysis by 2-DG also made it useful to treat cancer.[33]

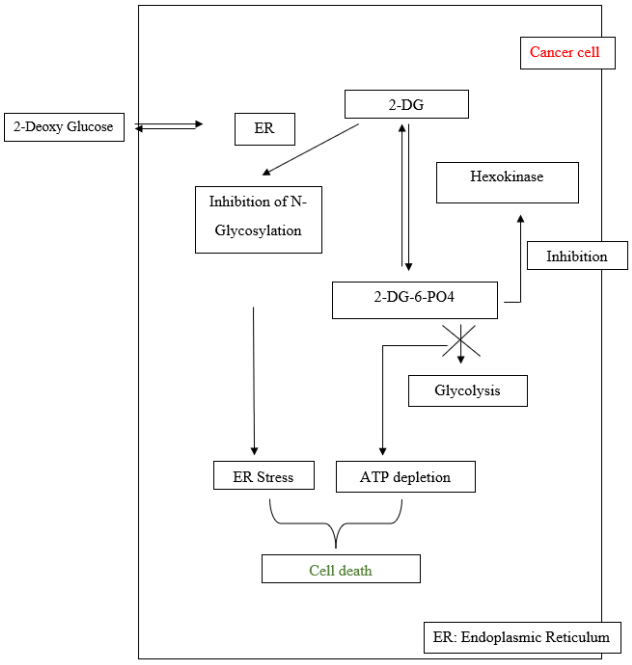

Figure: 2 schematically represents the mechanism of action of 2-DG

According to a study published in 2011, the toxicity of 2-DG in cancer cells is caused by the activity of the enzyme Aldo-Keto Reductase family 1, member B1 (AKR1B1).[34] The findings reveal that when 2-DG is reduced by AKR1Bs, it damages cancer cells by depleting their cofactor Nicotinamide Adenine Dinucleotide Phosphate (NADPH), which leads to the loss of glutathione and cell death. In some clinical studies, combining 2-DG and metformin results in considerable cell death, as well as a reduction in cellular ATP and prolonged activation of AMP activated Protein Kinase.[35] A study conducted in the year 2015 conclude that, 2-DG also promotes the tumour suppressor protein thioredoxin interacting protein (TNXIP) and inhibits cellular glucose uptake.[36] Figure 2: Diagrammatic representation of mechanism of 2-DG in cancer cell.

Adverse Drug Reactions Associated With 2-DG

In animal model studies conducted in the year 2012 states that, 2-DG has some negative side effects in addition to its therapeutic efficacy.[37] In this experiment, rats were given 1000mg/kg/day I.P. for 14 days. It has no discernible negative impact on spatial learning and memory, as demonstrated by a water maze trial. Another open field assessments in 2009 assert that 250mg/kg I.P was linked to a reversible decrease in exploratory behaviour.[38] In terms of clinical trials, a study performed in 2008 found that single intravenous dosages of 2-DG up to 200mg/kg have no significant side effects.[39] Another study conducted in 2013 found significant unfavourable effects of 2-DG[40] Fatigue, sweating, dizziness, and nausea were reported at doses of up to 63 mg/kg. They also found that 60 mg/kg of 2-DG per day was shown to cause QT prolongation – a severe cardiac condition. As a result, 60 mg/kg was chosen as an acceptable dose.[39] The most common side events were reversible hyperglycemia (100%), gastrointestinal bleeding (6%), and reversible grade 3 QTc prolongation (22%).[40]

2-DG conjugate as a novel drug for Covid-19

The Hyaluronic Acid - 2-Deoxy-D-Glucose (HA-2DG) Conjugate Acts as a Potential Targeted Drug Delivery Option for COVID-19 Treatment. To boost bioavailability, better localization, controlled release throughout the body, improve overall efficiency, and remove or reduce systemic toxicity, hyaluronic acid (HA) was covalently bonded to 2-DG to form HA-2DG conjugate.

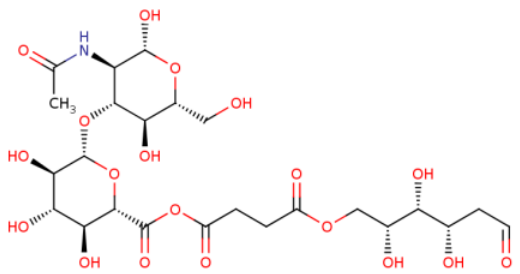

Figure 3: Structure of Hyaluronic Acid- 2-Deoxyglucose conjugate (HA-2DG)

The glucuronic moiety of 2-DG can be conjugated to hyaluronic acid via an ester bond between the 2-DG main C-6 hydroxyl group and the hyaluronic acid C5'carboxylic group (Figure 3: structural representation of HA-2DG). HA-2DG's binding method contains a viral virulence component, making it an effective therapeutic target for the treatment of COVID-19.

2-DG has recently been proven to inhibit the replication of the SARS-CoV-2 virus. The HA- 2DG conjugate showed greater binding affinity with all four examined SASR-CoV-2 viral targets (Mpro, RdRp, PLpro, and S protein) than the antimetabolite drug 2DG alone, according to a molecular docking research conducted in 2021. When 2-DG and HA-2DG were analysed for absorption, distribution, metabolism, and toxicity (ADMET), it was discovered that HA-2DG had lower toxicity than 2-DG alone. The study also revealed that the HA-2DG combination also has a number of advantages, including excellent drug delivery to CD44 variant isoform receptors in the lower respiratory tract and the highest interaction binding affinity with SARS-CoV-2 protein targets. Furthermore, the HA-2DG has superior biodegradability, biocompatibility and it is non-immunogenic. Due to its good antiviral activity, HA-2DG can be developed as a viable early-stage drug for the treatment of COVID-19. Additionally more in vivo and preliminary studies are needed to fully identify its activity and determine whether it can be used as a potent agent against COVID-19.[41]

Conclusion

2-Deoxy-D-Glucose can be used as a promising candidate in both virology and oncology. However, additional evidence and data are needed to clarify the precise mechanism and action of 2-DG in both COVID-19 and cancer, so more studies are needed to properly explain the features of 2-DG. 2-DG also had a number of side effects, which are unavoidable in the allopathic medical system. This paper will serve as an aiding tool for the medical community to fight against this pandamic. Many trials are indeed to be undertaken in the future to assess the risk benefit ratio of 2-DG in oncology and virology. 2-DG can surely evolve as a game changer in the realm of medical science.

Acknowledgement

We would like to express our thanks to the head, Department of Pharmacy Practice and our department staffs to their valuable suggestions and recommendations.

Conflict of Interest

There are no conflicts of interest to declare.

Funding Sources

There are no funding sources, what so ever, for this study.

References

[1]. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-HM, Lachmann G, *et al.,* The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med*. 2021; 9(6): 622-64.

[2]. Cheng G, Zielonka J, Dranka BP, McAllister D, Mackinnon AC, Joseph J, Kalyanaraman B. Mitochondriatargeted drugs synergize with 2-deoxyglucose to trigger breast cancer cell death. *Cancer Res*. 2012; 72(10):2634-44.

[3]. Abishek R, Arumuga VM, Prethi R, Priya M, Jothi TE. A review on: Repurposed use of 2 -de oxy-d-glucose as an adjunct therapy for covid-19 patients. *Int J of Pharm Clin Res*. 2021; 5(2): 28-34.

[4]. Kang HT, Hwang ES. 2-deoxyglucose: an anticancer and antiviral therapeutic, but not anymore a low glucose mimetic. *Life Sci*. 2006; 78(12):1392-9.

[5]. Desalvo J, Kuznetsov JN, Du J, Leclerc GM, Leclerc GJ, Lampidis TJ, *et al.,* Inhibition of Akt potentiates 2-DG–Induced apoptosis via down regulation of UPR in acute lymphoblastic leukemia. *Mol Cancer Res*. 2012; 10(7):969-78.

[6]. Aydogan B, Li J, Rajh T, Chaudhary A, Chmura SJ, Pelizzari C, *et al.,* AuNP-DG: deoxyglucose-labeled gold nanoparticles as X-ray computed tomography contrast agents for cancer imaging. *Mol Imaging Biol*. 2010; 12(5):463-7.

[7]. Aft RL, Zhang FW, Gius D. Evaluation of 2-deoxy-D-glucose as a chemotherapeutic agent: mechanism of cell death. *Br J Cancer*. 2002; 87(7):805-12.

[8]. Xi H, Kurtoglu M, Lampidis TJ. The wonders of 2-deoxy-d-glucose. *IUBMB Life*. 2014; 66(2):110-21.

[9]. Zhang Y, Huang F, Wang J, Luo H, Wang Z. 2-DG-regulated RIP and cFLIP effect on liver cancer cells apoptosis induced by TRAIL. *Med Sci Monit*. 2015; 10: 3442–3448.

[10]. Bost F, Decoux PA, Tanti J.F, Clavel, S. Energy disruptors: Rising stars in anticancer therapy? *Oncogenesis*. 2016; 5: e188.

[11]. Xi H, Kurtoglu M, Liu H, Wangpaitchitr M, Liu, X, *et al.,* 2-Deoxy-d-glucose activates autophagy via endoplasmic reticulum stress rather than ATP depletion. *Cancer Chemother Pharmacol*. 2011; 67: 899–910.

[12]. Jung CH, Ro SH, Cao J, Otto NM, Kim DH. mTOR regulation of autophagy. *FEBS Lett*. 2010; 584: 1287–1295.

[13]. Mizushima, N. Physiological Functions of Autophagy, in Infection and Immunity. *Springer Sci Rev*. 2009; 12: 71–84.

[14]. Feng, Y; He D, Yao Z, Klionsky DJ. The machinery of macroautophagy. *Cell Res*. 2014; 24: 24–41.

[15]. Cheong, H. Integrating autophagy and metabolism in cancer. *Arch Pharm Res*. 2015; 38: 358–371.

[16]. Muñoz PC, Ruiz RC, Almodóvar CR, Palacios C, López RA. Inhibition of Glucose Metabolism Sensitizes Tumor Cells to Death Receptor-triggered Apoptosis through Enhancement of Death-inducing Signaling Complex Formation and Apical Procaspase-8 Processing. *J Biol Chem*. 2003; 278: 12759–12768.

[17]. Xu RH, Pelicano H, Zhou Y, Carew JS, Feng L, Bhalla KN, *et al.,* Inhibition of glycolysis in cancer cells: A novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. *Cancer Res*. 2005; 65: 613–621.

[18]. Boutros J, Almasan A. Combining 2-deoxy-d-glucose with electron transport chain blockers. *Cancer Biol Ther*. 2009; 8: 1237–1238.
[19]. Valera V, Ferretti MJ, Prabharasuth DD, Chaimowitz M, Choudhury M, *et al.,* Is targeting glycolysis with 2-deoxyglucose a viable therapeutic approach to bladder cancer? *Int J Cancer Ther Oncol*. 2017; 5: 511.
[20]. Kim PJ, Lee DY, Jeong H. Centralized Modularity of N-Linked Glycosylation Pathways in Mammalian Cells. *Plos One*. 2009; 4: e7317.
[21]. Biberich, E. Synthesis, processing, and function of N-glycans in N-glycoproteins. *Adv Neurobiol*. 2014; 9: 47–70.
[22]. Kurtoglu M, Gao N, Shang J, Maher JC, Lehrman A, Wangpaichitr M, Savaraj, *et al.,* Under normoxia, 2-deoxy-d-glucose elicits cell death in select tumor types not by inhibition of glycolysis but by interfering with N-linked glycosylation. *Mol Cancer Ther*. 2007; 6: 3049–3058.
[23]. Berthe A, Zaffino M, Muller C, Foulquier F, Houdou M, *et al.,* Protein N-glycosylation alteration and glycolysis inhibition both contribute to the antiproliferative action of 2-deoxyglucose in breast cancer cells. *Breast Cancer Res Treat*. 2018; 171: 581–591.
[24]. Griffin TJ, Gygi SP, Ideker T, Rist B, Eng J, *et al.,* Complementary profiling of gene expression at the transcriptome and proteome levels in Saccharomyces cerevisiae. *Mol Cell Proteomics*. 2002; 1(4): 323-33.
[25]. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. *Oncogene*. 2006; 25(34): 4633-46.
[26]. Spivack JG, Prusoff WH, Tritton TR. A study of the antiviral mechanism of action of 2-deoxy-D-glucose: normally glycosylated proteins are not strictly required for herpes simplex virus attachment but increase viral penetration and infectivity. *Virology*. 1982; 123(1): 123-38.
[27]. Codo AC, Davanzo GG, Monteiro LB, De Souza GF, Muraro SP, Virgilio SJV, *et al.,* Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis dependent axis. *Cell Metab*. 2020; 32(3): 437-446.e5.
[28]. Bojkova D, Klann K, Koch B, Widera M, Krause D, Ciesek S, *et al.,* Proteomics of SARS-CoV2-infected host cells reveals therapy targets. *Nature*. 2020; 583(7816): 469-72.
[29]. Ardestani A, Azizi Z. Targeting glucose metabolism for treatment of COVID-19. *Signal Transduct Target Ther*. 2021; 6(1): 112.
[30]. Balkrishna A, Thakur P, Singh S, Dev S, Jain V, Varshney A, *et al.,* Glucose antimetabolite 2-deoxy-Dglucose and its derivative as promising candidates for tackling COVID-19: insights derived from in silico docking and molecular simulations. *Authorea Prepr*. 2020.19: 134-42
[31]. Neill OH, Doran S, Fraioli F, Nasoodi A. A twisted tale-radiological imaging features of COVID-19 on 18 FFDG PET/CT. *Eur J Hybrid Imaging*. 2020; 4(1):1.
[32]. *Ronak B.* India's Drug Regulator Has Approved DRDO's New COVID Drug on Missing Evidence. The Sciences. Updated on May 21, 2021. Assessed on September 10, 2021. India's Drug Regulator Has Approved DRDO's New COVID Drug on Missing Evidence - The Wire Science.
[33]. Kobayashi H, Nishimura H, Matsumoto K, Yoshida M. Identification of the determinants of 2-deoxyglucose sensitivity in cancer cells by shRNA library screening. *Biochem Biophys Res Commun*. 2015; 467(1):121-7.
[34]. Zhang SQ, Yung KK, Chung SK, Chung SS. Aldo-keto reductases-mediated cytotoxicity of 2-deoxyglucose: A novel anticancer mechanism. *Cancer Sci*. 2018; 109(6): 1970-80.
[35]. Cheong JH, Park ES, Liang J, Dennison JB, savachidou D, Nguyen CC, *et al.,* Dual inhibition of tumor energy pathway by 2-deoxyglucose and metformin is effective against a broad spectrum of preclinical cancer models. *Mol cancer ther*. 2011; 10(12): 2350- 2362.
[36]. Hong SY, Hagen T. 2-deoxyglucose induces the expression of thioredoxin interacting protein (TXNIP) by increasing O-GlcNAcylation–Implications for targeting the Warburg effect in cancer cells. *Biochem Biophys Res Commun*. 2015; 465(4): 838-44.
[37]. Ockuly JC, Gielissen JM, Levenick CV, Zeal C, Groble K, Munsey K, *et al.,* Behavioral, cognitive, and safety profile of 2-deoxy-2-glucose (2DG) in adult rats. *Epilepsy Res*. 2012; 101(3): 246- 252. 42.
[38]. Stafstrom CE, Ockuly JC, Murphree L, Valley MT, Roopra A, Sutula TP. Anticonvulsant and antiepileptic actions of 2-deoxy-D-glucose in epilepsy models. *Ann Neurol*. 2009; 65(4): 435-47.
[39]. Catena R, Bottoni P, Pontoglio A, Mastrototaro L, Giardina B. Glycolytic enzyme inhibitors in cancer treatment. *Expert Opin Investig Drugs*. 2008; 17(10): 1533-45.
[40]. Raez LE, Papadopoulos K, Ricart AD, Chiorean EG, DiPaola RS, Stein MN, *et al.,* A phase I doseescalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. *Cancer Chemother Pharmacol*. 2013; 71(2): 523-30.
[41]. Thirumalaisamy R, Aroulmoji V, Riaz K, Sivasankar C, Deepa M. Hyaluronic Acid - 2-Deoxy-D-Glucose Conjugate Act as a Promising Targeted Drug Delivery Option for the Treatment of COVID-19. *Int J Adv Sci Eng*. 2021; 7(4):454-460.