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# 2-Deoxy-D-Glucose and COVID-19

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## ABSTRACT

*Viral infections are difficult to treat because of the viruses' complex structure and metabolism. They can also hijack the metabolism of the host cell, mutate and adapt to harsh environmental conditions. SARS-CoV-2, a new coronavirus, has considerably more resistant characteristics, making eradication even more challenging.*

*Following the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), a third highly pathogenic coronavirus, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged at the end of 2019, causing a pandemic, increased panic and drew worldwide attention. Coronaviruses (CoVs) are a highly diverse family of enveloped positive sense single stranded RNA viruses. Because viruses require substrates and energy from the host for their construction and replication, taking advantage of the increased glycolytic flow for these functions could be a key aspect of viral infections.*

*SARS-CoV-2 virus can be stopped from replicating by reducing the substrates available for structural integration. 2-Deoxy-D-glucose is one such molecule that limits substrate availability and has recently gained a lot of attention (2-DG) infection with SARS-CoV-2 cause's glycolysis, reduces mitochondrial activity and damages infected cells. 2-DG administration can stop viral replication by inhibiting enhanced glycolytic flux and other metabolic activities. The drug can have adverse effects on different systems of body as it affects the normal metabolism of the cells because it targets cells non-selectively, in a dose dependent manner. This article gives information about the mechanism of action of 2-Deoxy-d-glucose on the virus and host cell and its use in this pandemic.*

**Key words:** 2-Deoxyglucose, Hyperglycaemia, SARS-CoV-2, COVID-19

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## INTRODUCTION

4,876,601 people succumbed to death till October 2021, owing to the incredibly transmissible virus form the family of Coronavirus led to the pandemic. The disease was entitled as COVID-19 disease by the world health organization on January 2020. The disease was stimulated by severe acute respiratory syndrome coronavirus 2, which was abbreviated as SARS-CoV-2. This created an unusual panic situation worldwide. This disease notably most profound crisis situation causing pandemic after scourge of 1918 influenza contagion. To find a definitive cure for the disease many researches and drug tests have been conducted as the number of infections continues to rise around the world. However, there is a paucity of effective medications.

The world saw the mount of the COVID-19 disease cases named as first wave in April 2020, which was when the DRDO scientists stationed at INMAS performed a lab study on 2-DG molecule to make this coronavirus as deficient its actions. This study was enacted with the coaction of centre for cellular and molecular biology situated at Hyderabad. The manufacturer was Dr. Reddy's Laboratories working with DRDO scientists. With the progress of the study in lab, found out that the molecule of this drug showed replication of virus, which meant that chemical needed for halting the COVID-19 disease progression was ciphered out. Results presented by this lab experiment contrived that Central Drugs Standard Control Organization (CDSCO) of the Drugs Controller General of India (DCGI) approved a Phase-II clinical trial in May to October 2020 with 110 patients on board. On-going trials were shows the good prognosis of the study and later instituted that DRDO's drug is safe against the COVID-19 disease. The recovery was appreciable in view of the other drugs used to fight for the disease. Phase II trials had subset of phases of trials, which were supervised in six and eleven hospitals throughout the whole nation. Phase II and Phase IIb were the subset of Phase II trials answers licensed DCGI to move forward with Phase III trials in November 2020. By the end of March 2021, total sample size of 220 patients was approved for the Phase III trials. All the above accepted patients were originated from states like Uttar Pradesh,

West Bengal, Rajasthan, Gujarat, New Delhi, Maharashtra, Telangana, Tamil nadu, Karnataka, accounting of 27 COVID-19 hospitals. Day 3 of the treatment in trial reflected the positive recuperation and free from appendage Oxygen supply *i.e.,* 42% *vs.* 31%. More than 60 years old benefitted the most after the administration the drug. With loads of data after the trial and good to proceed from the results of the trials, DCGI empowered the government for the Emergency Use on 1st May, 2021. This drug was approved for the patients with moderate to severe group only as a supplementary therapy.

## LITERATURE REVIEW

A high number of patients in the on-going second COVID-19 wave are suffering from severe oxygen dependency and require hospitalization. Because of the drug's mode of action in infected cells, it is predicted to save many lives. COVID-19 patients spend less time in the hospital conditioned by this drug effectively.

Infection caused by SARS-CoV-2 virus has demonstrated a two-way directional bond amidst upheaved glucose levels in the blood [1,2]. A high blood sugar levels with its cognate absorbs great percentage in the cells infected with virus for instance cancer cells [3,4]. There are many accounted diagnostic markers for the cancer and one of the most eminent markers is Fluorodeoxyglucose F 18, correspondingly abbreviated as (18F) FDG or 18F-FDG, which contains two group of deoxy molecule, performs as radiotracer, used in imaging mode of positron emission tomography means PET scan as the medical use. Glycolysis stifled by means of this synthetic glucose analogue by so-called 2 deoxy-D-glucose. Synchronizing the crucial conduit in view of strengthening the structure, process and duplication, SARS-CoV-2 virus hence manages the course of infecting the cells of the human being or an animal. Therefore, its favourable in the management of cancers and viral diseases [5,6].

Because the drug prevents the replication of SARS-CoV-2 in infected monocytes, it may be used to treat COVID-19 in addition to the commonly used drugs. However, due to its side effects, its therapeutic utility is limited based on pre-clinical data on cellular metabolism [7-10].

With the help of GLUT transporters and glycolysis done intercellular glucose produced is stalled by 2DG. Controlling the depletion of nucleotides, pyruvate, ATP, NADH by inhibition done by glycolysis, which needed for phosphorylation of many intermediary metabolites through the sustainment of the metabolic pathways.

ATP diminution leads to switching of the catabolises with the necessary process of halting anabolic cellular mechanisms; moreover it's associated with necrosis leading to cell death by the weakening of membrane and discharging the extracellular ATPs. Fore mentioned processes concludes the activation of the immune system in greater amount causing in the abundance of the inflammatory processes named as cytokine storm and ARDS in the COVID-19 disease [11].

Hexokinase II is an enzyme which tends to surge the glucose phosphorylation by making the ATP within the mitochondria, subsequently creates anti-apoptotic impact with reducing molecules activities [12]. As there are two paths of inhibition namely intrinsic and extrinsic pathways respectively. These pathways are threatened by process of apoptosis *via* intrinsic pathway and also glycolysis *via* extrinsic pathways.

With all the consequences, glycolysis restraints and using up all ATP, there is chance of affecting by modifying the post translation independently by the 2DG. Hence, it reverses the key molecules (glycosylation mediated packaging, trafficking). N-glycosylation is mandatory for the viability, as confirms the development of the proteins, which is under the stress for not able enhance protein manifestation in the area called endoplasmic reticulum, owing to impaction to autophagy causing apoptosis of the cells. By the action of apoptosis, changes are seen after the protein production works with the aim for programmed cell death in the ATP rich ecosystem under the ample source of oxygen [13,14].

The course of arresting the process of cell cycle where it is no longer involved in doubling and dividing of the cells, the disruption of the balance between the free radicals production and defence system of the antioxidants and with the out functioning of cells to comprehend the glucose, all organized by Thioredoxin Interacting Protein (TXINP) [15]. "2-DG" drug also bring about O-glycosylation by inducing TXNIP but the method is still not clearly grasped but is clearly under the influence of the chemicals in the drug over the Carbohydrate Response Element (ChoRE).

## DISCUSSION

### Viral load and blood glucose

Novel coronavirus precedence the COVID-19 disease had affected firmly on the people who were obese and pertained to resistance to the insulin which can be concluded to diabetes type II. People enduring with DKA and hyper osmolality or freshly developing diabetes with no history of diabetes have also been associated.

Excess of sugar in blood has been highly appreciated in SARS-CoV-2 infection. The treatment containing use of steroids intensifies the resistance of insulin, the body responses to the high stress for grave sickness, not proper working of the Beta cells found in the pancreas and the steroid use. COVID-19 escorts due to insulin resistance happen to be the primary cause for the high blood sugar associated with adipose tissue dysfunction.

Diabetes causes cellular malfunction and cell death as a result of increased glucose absorption. HK-II facilitates glycolytic entry which reduces the working of the cells with no changing of the transcription in diabetics. Amplified stimulation of the constantly moving in and out of the glucose activates hexamine, protein kinase c and also dicarbonyl stress pathways.

**Effect of 2-DG on viruses**

Misusing the proliferation of the glycolytic flux has been worked as one of the noteworthy trait of various viral infections. As every process needs medium to get transferred like that viruses gets multiplied and energy derived *via* host. 2-DG has been accounted for halting the reduplicating of the viruses which are enveloped such as influenza, measles, semliki forest, sindbis virus, CMV virus, HP virus and others [16].

CMV stimulates CaMKK1 and influences viral replication and glycolysis. With the infection causes increase in inflammatory cells which engages in increasing the glucose uptake with increased activities of metabolism. Infections caused by the viruses often make blood glucose on higher level even the herpes virus has been out of the host.

Augmented metabolic activity with enriched glucose uptake has been resulted due to inflammatory cells. With many conditions, the infections like herpes simplex virus causes high glucose in the blood also the infectious agent id not present in the cells. With this situation created by the infectious agent present in the cells show that there was increase in the alterations of the cell metabolism. The need of drug to inhibit the glycosylation and multiplication of the herpes virus was done with the help 2 DG in the infected cells [17-19].

The route which is accounted for the lipid synthesis which required for the entry of the virus after getting release from the cells moreover the intermediates for the citric acid generation is shown the glycolysis [20]. For making the 2-DG to work against the COVID-19 disease, preventing glycolysis from occurring and changes that has been occurred post production protein called post translational modification has shown the great influence on the halting the augmentation of the viruses.

**2-Deoxy-D-Glucose and functioning of cells**

By exception in few trials, 2-DG has been shown to be safe in several pre-clinical researches [21]. Human investigations with limited data demonstrate that it is well tolerated. However, because the drug might disrupt the normal chemical reactions in the metabolism of the cells, by the administration in people is risky due to the possibility of side effects that could result from extrapolating findings from pre-clinical research.

The medicine has the potential to have negative effects on the nervous, cardiovascular, endocrinological, and haematological systems.

In the context of hypoxia, 2-DG can provide neuro protection to central nervous system neurons, but it also induces an increase in cell death. The Central Nervous System's macrophages are microglial cells (CNS). 2 DG inhibits glycolysis in microglia *in vitro*, causing cell death due to ATP depletion.

This microglia specific impact of 2-DG is owing to their increased reliance on glycolysis, particularly during activation. Neurons, on the other hand, rely heavily on mitochondria to meet their ATP requirements [22,23]. In animal models of disorders with microglial activation linked neuronal loss Alzheimer's disease, Parkinson's disease, stroke, trauma, meningitis and epilepsy-neurons are relatively untouched by the drug's actions. However, the neuro protection isn't complete, and increased neuronal death has been reported in pathological conditions linked to hypoxia, such as stroke, vascular dementia, and trauma. Metabolic encephalopathy (6.8%), seizure (1.6%), stroke (1.9%) and hypoxic damage (1.9%) were the most prevalent neurological diagnoses (1.4%). No incidences of meningitis or myelitis were found, and CSF RT-PCR testing was negative.

This suggests that COVID-19 infection causes CNS involvement as a result of SARS-CoV-2-induced systemic dysfunction. The use of 2-DG can possibly alleviate COVID-19-related seizures.

The medicine has the potential to harm the peripheral nervous system. Due to increased mortality and substantial effects on the peripheral nervous system, a clinical trial including the glycolysis inhibitor dichloro acetate was prematurely halted.

**Cardiovascular effects:** In rats which were experimented showed the signs of toxicity on heart, pheochromocytoma and in some cases death of the rats when they were administered as a sustained dose of 20 to 300 mg/kg. Hence, lethal effect of the drug on the heart was proven to reversible post 60 days of abstinence. This had a tremendous effect on the function of the heart showing regression which was monitored by the cardiac investigative tests like N-terminal pro b-type natriuretic peptide (NT proBNP) and Brain Natriuretic Peptide (BNP). ECG predicted T-wave flattening and also QT prolongation with reversibility with 24 hours.

**Endocrinological effects:** 2 DG has the process of affecting at the cellular level by depriving with lack of glucose but has showed the impairment causing negative feedback to the central and autonomic mechanisms, which could be dangerous for the human life. Hence, Beta blockers were been prescribed. Pheochromocytoma could be because of the some alteration in HIF alpha pathway and mitochondrial starvation provoked by 2DG.

**Haematological effects:** All the issue for mentioned is all due to the increased glycolysis and glycogenolysis, by which it leads to activation of platelets and inversely degranulation occurs inside the blood cells [24].

**Arsenic compounds:** These compounds are known to have an effect on glycolysis by stopping it, with the help weakening the mitochondrial respiration. If the arsenic compounds are ingested in any form for one to four days could lead to acute and chronic toxicity respectively. But is dose dependent. This toxicity has linked to symptoms like acute discomfort in the stomach, fluid in the lungs, failure of the lungs, cardiomyopathy, coagulation issues and neuropathy [25].

**Use of optical imaging**

2-deoxy-d-glucose has a history of stating for fluorescent in lieu of imaging agent as focused optical imaging. Fluorodeoxy glucose has been repeatedly associated with PET scans, which works by emitting gamma rays. In imaging like PET scans, 2-hydrogen of 2-DG is changed with positron-emitting isotope fluorine 18. This mechanism is used to find out the source of the cancer, where there an uptake of glucose from the cancer tissues.

**2-DG COVID-19 medicine price**

Price was depended on the level of production notified by Dr. Reddy's Laboratories. Price was announced between 990 rupees per sachet. Such range of price feasible for the common man. This price was subsidized by the government across the whole nation. One box of the drug will be containing 10 sachets. The drug will be used only in the hospitals and institutions. Per sachet will contain 2.34 g.

## CONCLUSION

2-Deoxyglucose (2-DG) inhibits glycolysis through mechanisms that are both dependent and independent. *In vitro* investigations have shown it to be effective at preventing viral replication. However, there are concerns about the drug's negative effects on the heart, neurons, adrenal medulla and platelets when used in humans, especially since it hasn't been thoroughly investigated for therapeutic uses.

Because it depletes energy storage and interferes with cell metabolism, the drug has a limited application in the treatment of stroke, hypoxic ischemic encephalopathy, and serious condition. As a result, 2-DG should be administered with caution in modest dosages and for a short period of time after careful examination of the clinical situation and risk benefit ratio in each instance.

By the virtue of the various medicines worked in many studies has helped for the treatment. Foresight of 2-DG, the drug could be used in treating of the diseases such as stroke, encephalopathy's, critical illness as its character of removing the stores of the energy in the metabolism of the cells. These drugs needed for further use in many randomized control studies for making them possible to include in standard treatment and making as a successful drug for COVID-19 disease. The drug will help to reduce the effect of the COVID-19 disease and will protect humans and save lives.

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