

(REVIEW ARTICLE)

## A review on the 2-Deoxy-D-Glucose (2-DG) in COVID-19 disease

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GSC Biological and Pharmaceutical Sciences, 2022, 19(03), 008-014

Publication history: Received on 30 April 2022; revised on 01 June 2022; accepted on 03 June 2022

Article DOI: <https://doi.org/10.30574/gscbps.2022.19.3.0218>

### Abstract

This has given a lead to study the role of 2-deoxy-D-glucose (2DG) against COVID-19 (corona virus) disease. We hereby would like to briefly discuss the concept and rationale behind the use of 2DG COVID-19. Virus infections can cause cell damage in many ways. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a cause of the current COVID-19 pandemic, has been extensively studied so far to investigate its pathophysiology and evaluate its impact on the metabolic system of human cells. The Drug Controller General of India (DCGI) has given emergency use approval to 2-deoxy-D-glucose (2-DG), an anti-Covid drug developed by INMAS, a DRDO lab, in collaboration with Dr Reddy's Laboratories (DRL), Hyderabad.

**Keywords:** Covid; 2-deoxy-D-glucose (2DG); Corona virus; Drug Controller General of India (DCGI)

### 1. Introduction

Currently, COVID-19 patients are treated based on the disease severity. In India, moderate to severe category patients are treated with oxygen support and intravenous steroids. Drugs like remdesivir and tocilizumab are only suggested to be used in selected patients [All India Institute of Medical Sciences (AIIMS) protocol dated 17 May 2021]. Various other drugs have been tried across the globe with different outcomes. On similar lines, 2-deoxy-D-glucose (2DG) has been approved by the Indian Council of Medical Research (ICMR) on 1<sup>st</sup> May 2021. During the 1<sup>st</sup> wave, India was able to successfully contain the spread and death toll to a significantly low level [1]. This drug has come at a time when India is going through the 2<sup>nd</sup> wave of the COVID-19 pandemic with worrisome morbidity and mortality figures. As of 21<sup>st</sup> May 2021, India is reporting almost 300,000 to 350,000 new COVID-19 cases on daily basis with close to 1000 deaths per day. Hence, scientists, physicians, and patients are looking forward to this new potential drug that might change the trajectory of the COVID-19 pandemic in India.

#### 1.1. Diagnostic role

2-DG is essentially a glucose molecule in which, the 2-hydroxyl group gets replaced by hydrogen. Due to this chemical replacement, 2DG is not able to enter glycolysis and contribute to ATP production. DG otherwise can be attached to various radioactive substrates and currently is being extensively used in various diagnostic tests and laboratory studies. For instance, in a positron emission tomography (PET) scan study, 2-DG is commonly used as a chemical dye. When a PET study is done in a patient with suspected cancer, 2-DG is preferentially taken up by tumor cells in an excessive amount due to the high metabolic rate. The radiolabeled 2-DG allows these cancer cells to glow prominently to be picked up in imaging.

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### 1.2. Anticancer role

The Warburg effect is one of the well-studied concepts in cancer biology which suggests a cause-effect relationship between cancer development and the increased aerobic glycolysis within the cells [2]. 2-DG is considered to interrupt the glycolysis and hence block the subsequent growth of cancer cells [3-4]. In addition to this, 2-DG reduces glycosylation and inhibits the pentose phosphate pathway which indeed inhibits angiogenesis, and increases autophagy and apoptosis of cancer cells [5].

### 1.3. Antiviral role

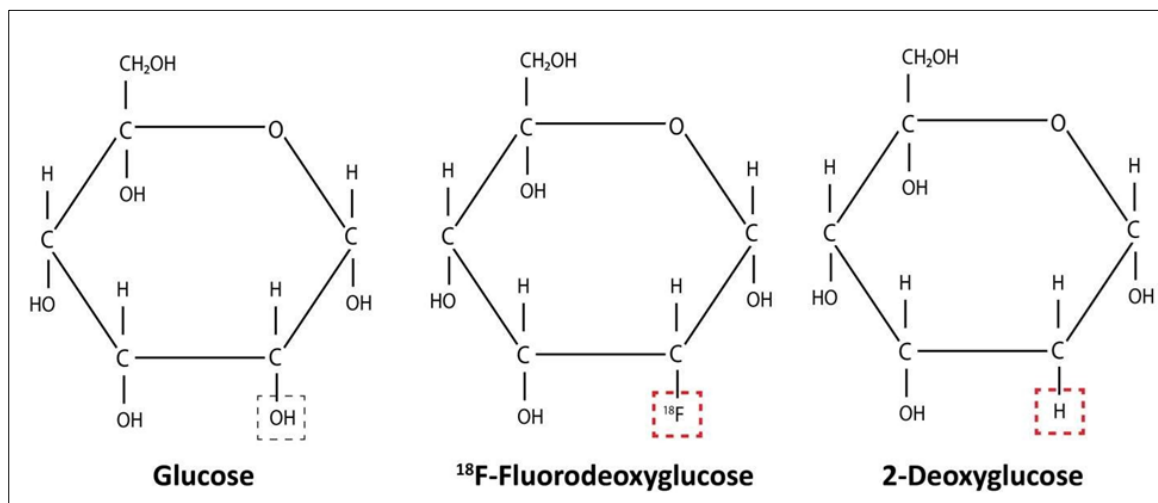
There is already enough literature and studies on the potential role of 2-DG for its antiviral activity [6-7]. *In vitro* studies on the herpes virus have shown that 2-DG affects the early stages of the viral replication cycle including reduced cell penetration by the herpes virus in presence of 2-DG.

## 2. 2-DG in COVID-19

Although the vaccine is available now, and there is a mass campaign going on in India and other countries to vaccinate as many people as possible in the shortest time. However, vaccination with two doses with a duration of at least 3–4 weeks and a huge population are a few of the major hurdles ahead which demand to still aggressively find alternative, effective, and safe drugs to treat symptomatic patients with COVID-19. Remdesivir, tocilizumab, plasma therapy, and many other investigational drugs have been tested and are currently being used against COVID-19 with variable outcomes [8-9]. 2-DG can be considered as another attempt by scientists to fight against this deadly virus. Interestingly, a recent *in vitro* study by Cov. Showed that increased glucose levels and glycolysis promote SARS-CoV-2 infection [10]. They also noted that to have an upregulation of many glycolysis-associated genes in bronchoalveolar lavage (BAL) monocytes of COVID-19 patients. With these findings, Condo *et al.* proposed that at least in monocyte cells, increased glycolysis is specific to SARS-CoV-2 and could be considered as a potential pathway to target.

### 2.1. Mechanism of action

2-Deoxy-d-glucose (2-DG) is an analogy of glucose (Fig 1) that causes competitive inhibition of the rate-limiting enzyme - Hexokinase. This inhibition induces phosphorylation of glucose to 2-Deoxy-D-glucose-6-phosphate (2-DG-6-P). 2-DG-6-P acts as an allosteric and competitive inhibitor of Hexokinase, and its accumulation also inhibits the enzyme - Phosphoglucosomerase [11-12]. Thus, 2-DG can inhibit glycolytic flux, although it can influence multiple other cellular pathways



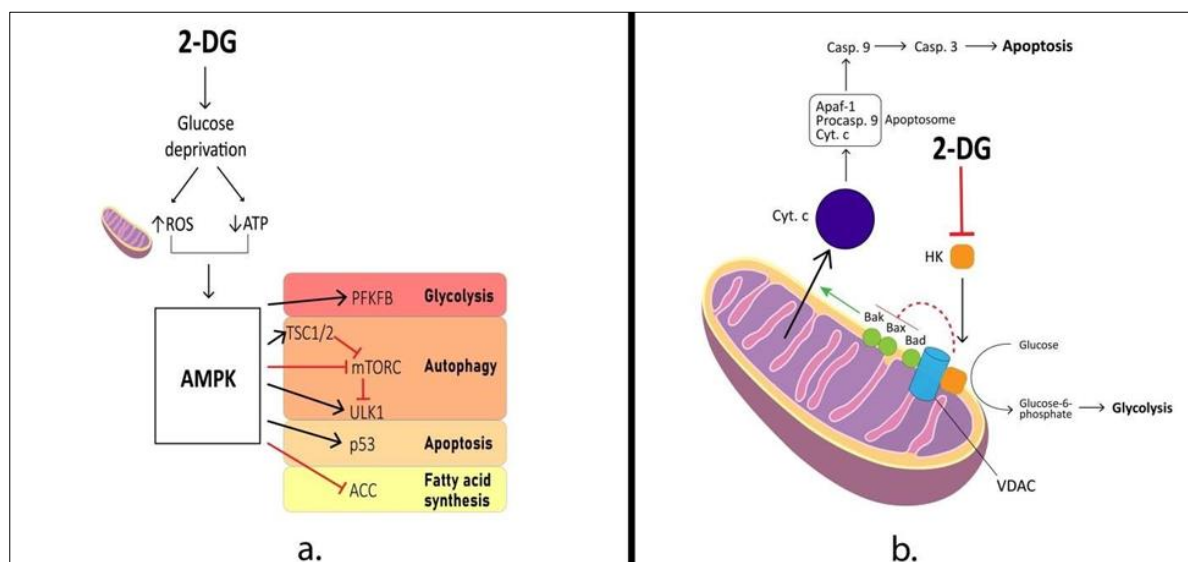
**Figure 1** [<sup>18</sup>F]-Fluorodeoxyglucose and 2-Deoxy-d-glucose are structural analog of glucose that differ on the second carbon in their structure

### 2.2. Inhibition of glycolysis, pentose phosphate pathway, and mitochondrial function

2-DG inhibits the cellular uptake of glucose by glucose transporters (GLUT) and its intracellular utilization by glycolysis. Inhibition of glycolysis depletes ATP, NADH, pyruvate, and nucleotides needed to phosphorylate multiple intermediary metabolites and sustain downstream metabolic pathways.

The depletion of ATP causes catabolic switching while inhibiting the anabolic cellular processes (Figure 2a.). In addition, intracellular ATP depletion is also associated with necrosis as the major pathway of cell death due to membrane instability and extracellular ATP release. These events can result in over-activation of the immune system leading to cytokine storm and acute respiratory distress syndrome (ARDS) in COVID-19 [13].

Glycolysis and apoptosis are closely linked, but the association is poorly understood. Localization of Hexokinase II (HKII) to mitochondria facilitates phosphorylation of glucose by ATP generated inside mitochondria and also has an anti-apoptotic effect by inhibiting the activity of some molecules (Figure 2b.) [14]. Hexokinase inhibition can thus induce apoptosis of the cells through the intrinsic pathway by destabilization of mitochondrial complexes. In addition, inhibition of glycolysis results in apoptosis through the extrinsic pathway and autophagy. [12].



**Figure 2** 2-DG impacts cell metabolism and induces apoptosis

- 2-DG causes glucose deprivation to decrease ATP and increase ROS production. As a result, AMPK is activated to increase cell metabolism in favour of increased catabolic activity. It is achieved through increased glycolysis by activating PFKFB and decreased fatty acid synthesis by inhibiting ACC. In addition, activated AMPK increases autophagy through ULK1. It also increases the expression of the tumour suppressor gene p53 to cause apoptosis.
- Hexokinase is mobilized from the cytosol to mitochondria to associate with VDAC. This association inhibits the activity of pro-apoptotic molecules-Bak, Bad, Bax. Activation of these pro-apoptotic molecules can cause apoptosis through the release of cytochrome c into the mitochondria. 2-DG induces apoptosis by inhibiting the anti-apoptotic function of Hexokinase.

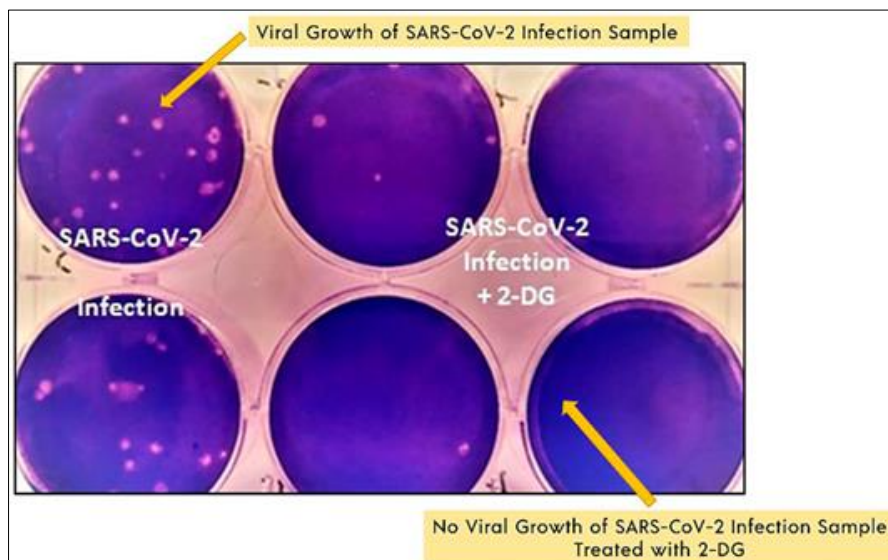
ROS: Reactive oxygen species; AMPK: AMP-activated protein kinase; PFKFB: 6-phosphofructo-2-kinase/fructose-2,6bisphosphatase; TSC: Tuberous sclerosis complex; mTORC: mammalian target of rapamycin complex; ULK: Unc-51 like autophagy activating kinase; ACC: Acetyl CoA carboxylase; HK: Hexokinase; VDAC: Voltage-dependent anion channel; Bad, Bax, Bak: proapoptotic molecules; Cyt.c: Cytochrome c; Casp. Caspase.

### 3. Preclinical and Clinical Development

2-DG is consumed by the SARS-CoV-2 contaminated cells. However, it is unclear whether 2-DG has the ability to destroy or damage normal cells or whether it has any effect at all on them. When weighing costs and advantages, the most critical question is whether the benefits outweigh the risks. On critical analysis, it can be stated that there are demonstrated benefits of 2-DG and that they outweigh the risks; hence, it is currently being provided to individuals with mild to severe COVID-19 infection. These patients have a significantly better chance of survival treated with 2-DG than people who receive traditional medications [15].

“Defence Research and Development Organisation (DRDO)” took the lead in designing an anti-COVID-19 medicinal implementation of 2-DG. INMAS-DRDO scientists, with the assistance of the “Centre for Cellular and Molecular Biology

(CCMB)", Hyderabad, performed different lab experiments during the first wave of COVID-19 pandemic in April 2020 that showed 2-DG was effective against the SARS-CoV-2, inhibiting viral development [16] "Drug Controller General of India and Central Drugs Standard Control Organization approved Phase-II clinical trials of 2-DG in COVID-19 patients in May 2020. DRDO and its business partner, Dr Reddy's laboratories, have begun clinical trials to assess safety and effectiveness of 2-DG in COVID-19 patients. (Fig 3). [15].



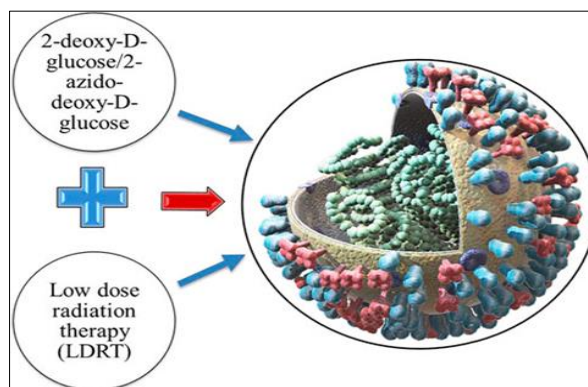
**Figure 3** SAR-CoV-2 Infection Sample

2-DG is stable in patients with COVID-19 and shows substantial progress in their rehabilitation in phase II clinical trials (including dose-ranging) performed from May to October 2020 [17].

### 3.1. Phase IIa

Human clinical trials were conducted in 6 hospitals, whereas phase IIb clinical trials (dose-ranging) were conducted in 11 hospitals worldwide. A phase II study was carried out in 110 COVID-19 patients. In terms of effectiveness, those who were given 2-DG had a quicker symptomatic relief compared to those treated with standard of care (SOC) on a variety of endpoints [18]. Comparing the median time for achieving normalization of basic vital sign factors to the SOC, a marginally favorable pattern (2.5 days difference) was observed. Based on the positive outcomes, DCGI approved phase III clinical trials in November 2020.

### 3.2. Phase III



**Figure 4** A Comprehensive look at covid-19

The phase III human clinical trial in 220 patients was conducted between December 2020 and March 2021 at 27 COVID-19 hospitals in the states of Uttar Pradesh, Delhi, Gujarat, West Bengal, Maharashtra, Rajasthan, Telangana, Andhra Pradesh, Tamil Nadu, and Karnataka. In comparison to SOC, a greater proportion of patients with in 2-DG arm proceeded



symptomatically and many were free of mechanical ventilation reliance by day 3 (42 percent vs. 31 percent). An identical pattern was noted in the case of patients over the age of [18]. Various potential side effects of 2-DG are reversible hyperglycaemia, gastrointestinal bleeding, and QTc prolongation [18]. Hyperglycaemia may also worsen, particularly as the majority of COVID-19 patients are also on large dosages of steroids [19]. The major loophole of the current phase II ( $n = 110$ ) and Phase III ( $n = 220$ ) clinical trial study data is very limited study population. Individuals with multi-organ dysfunction, ARDS, and those on mechanical ventilation were also omitted from the trial. Individuals with any type of chronic comorbidity were also barred from participating in the trial.

#### 4. Theragnostic Role of 2-DG in Management of Cytokine Storm in COVID-19

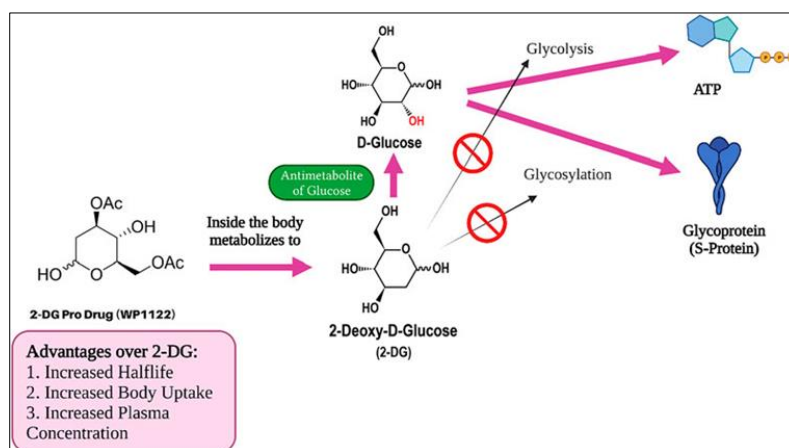
2-DG has also proven to be a polypharmacological agent for COVID-19 therapy, due to its role in the glycolytic pathway, interaction with viral proteins, and anti-inflammatory activity [21]. Verma et al. conjectured that 2-DG could enhance the efficacy of low-dose radiation therapy (LDRT) in the treatment of COVID-19 pneumonia. [22]. Furthermore, the azido analogue of 2-DG, 2-azido-2-DG, has the ability to trigger catastrophic oxidative stress in a short time in severely ill COVID-19 patients [22].

Low dose radiation therapy can decrease the cytokine storm in COVID-19 patients owing to its capability to induce anti-inflammatory responses. Its pro-inflammatory assisted immune responses in patients infected with SARS-CoV-2 has been advocated to be an efficacious option for COVID-19 pneumonia therapy. Fig 4 although, the timing of LDRT treatment is the most crucial factor as it may influence moderate versus severe conditions differentially. Appropriately, numerous LDRT protocols for COVID-19 patients are being evaluated with promising preliminary outcomes [23].

##### 4.1. 2-Deoxy-D-Glucose Prodrug (WP1122)

Moleculin Biotech Inc., in collaboration with Texas University (United States), has synthesized and evaluated a 2-DG prodrug candidate, WP1122, and its analogs for COVID-19 treatment. The main reason behind using this prodrug approach was that 2-DG does not possess “drug-like properties”. It metabolizes quickly (has a short half-life) and fails to provide the required concentration levels in organs and tissues. Principally, the achievement of sufficient concentration of 2-DG inside target organs and tissues to inhibit viral replication has not been possible in patients [24]. Hence, WP1122 with improved drug-like properties

Fig 5 is a promising analogue of 2-DG as a new anti-cancer agent, in addition to improving those with COVID-19.



**Figure 5** It is a promising analogue of 2-DG as a new anti-cancer agent

This chemically modified 2-DG is transformed into pharmacologically active 2-DG in the body following administration. Fig 4 the scientists have already proven *in vivo* that WP1122 reaches a much higher concentration in tissues and organs compared to 2-DG alone. Interestingly, the level after WP1122 administration is nearly twice as much its half-life while the peak plasma concentration increases by almost three times. When 2-DG is delivered *via* WP1122, it provides a much higher concentration of 2-DG in the organs and tissues *in vivo*, as compared to when it is given directly [26]. However, the greatest improvement seen is in the organ uptake and its potency. Moleculin Biotech’s previous work using WP1122 in cancer, even before the arrival of COVID-19, showed that WP1122 was 10 times more potent than equimolar doses of 2-DG alone. Recently, they have planned a clinical trial of WP1122 for COVID-19 [26].

## 5. Conclusion

Targeting glucose metabolism may offer new practical antiviral approaches for the treatment of mild to severe SARS-CoV-2 infection, especially in individuals with metabolic diseases. The 2-DG was designed to treat critically ill patients with COVID-19 in recent clinical trials in India. The Indian drug authority approved 2-DG as emergency use, which is available in powder form in sachets for oral route administration as an adjunct therapy. It builds up in virus-infected cells, prevents viral synthesis and energy output, and thereby inhibits viral replication. Its selective aggregation in the infected cells distinguishes this compound. Another promising approach is to use the combination of 2-DG and its derivative agents with different treatment modalities to inhibit the life cycle of the virus. This may slow down drug resistance development and decrease the effective concentration of individual drugs, reducing possible adverse effects. The findings are premature, and the individuals who will get 2-DG will need to be closely monitored. The creation of an online data repository to record the efficacy and adverse effects of 2-DG would be extremely beneficial in integrating data on 2-DG usage in COVID-19 illness. A multicentric investigation with a bigger population and from diverse geographical locations is needed to corroborate the preliminary results.

## Compliance with ethical standards

### *Acknowledgments*

The authors are thankful to Dr. Prashant K. Deshmukh, Principal, Dr. Rajendra Gode College of Pharmacy, Malkapur M.S., and India-443101 for providing the research facilities and encouragement.

### *Disclosure of conflict of interest*

The authors declare that there is no conflict of interests regarding the publication of this article.

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