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A review on: Repurposed use of 2-deoxy-d-glucose as an adjunct therapy for covid-19 patients

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ABSTRACT

2-Deoxy-D-Glucose with its long run history as a trialling anti-cancer agent has now approved for the management of moderate to severe corona positive patients in India. So far 218 clinical trials are going on in oncology using this drug as intervention or else as adjunct. 2-Fluro-Deoxy-D-Glucose an analogue of 2-Deoxy-D-Glucose is also being used as a radiotracer. Glucose is the source of energy for all cells in human body. As an anti-glycolytic agent, 2-Deoxy-D-Glucose put the high glucose utilizing neoplastic cells at starvation and leads to autophagy. It can also destroy high glucose demanding healthy cell like neurons is also a matter of concern. The same anti-glycolytic property is responsible for halting the pathogenesis of Severe Acute Respiratory Syndrome Corona Virus-2.It is noteworthy that the drug can also reduce oxygen dependence in active corona patients. This review collectively examines the anti-cancer and anti-viral nature of 2-Deoxy-D-Glucose. It epitomises the pharmacodynamic potential of the drug in both oncology and virology. Listing out clinical trials conducted so far using this drug as an intervention in both oncology and virology and shedding light towards the adverse effects of this drug are also important objectives.

Key words: COVID-19, 2-Deoxy-D-Glucose, SARS-CoV-2, Cancer, Clinical trials, Adverse effects.

INTRODUCTION

Severe acute respiratory syndrome corona virus-2 has emerged as one of the greatest health crisis since 2019.[1] First case of COVID-19 was identified in Wuhan, China in the month of December 2019. Later it has spread to 220 countries across the world as of April 2021[1]. At present India has been recording more than 300,000 cases per day.[2]To control the ravaging widespread of the disease, government of India is taking many proactive measures. As a ray of hope in the abatement of COVID-19, Drug Controller General of India gave approval for the emergency use of 2-deoxy-D-glucose as an adjunct therapy for moderately and severely infected corona patients. The drug was developed by Defence Research and Development Organization, in collaboration with Dr. Reddy's laboratories and approved on May-8, 2021. 2-DG is a glucose analogue. Before the repurposed approval

for COVID-19, 2-DG has been trailed in targeting cancer cells across the world. It has an activity of bringing cell death by inhibiting glycolysis.[3] Results also show that there is an increased uptake of 2-DG by cancer cells and hence it can also be used as a cancer cell marker.[4] Hence 2-DG disrupts glucose metabolism and protein glycosylation it also can be a good candidate against microbial infection.[5] This review exemplifies the role of 2-deoxy-D-glucose as a promising candidate for targeting neoplastic cells and also as a new candidate for tackling ongoing and unprecedented COVID-19 pandemic.

STRUCTURE OF 2-DG:

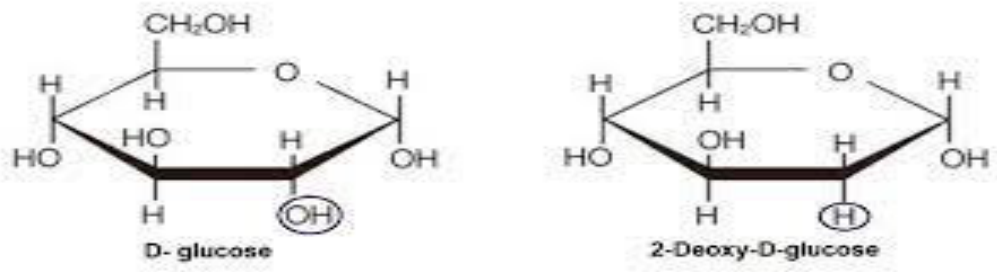

Figure.1 compares the structure of glucose and 2-Deoxy-D-Glucose.

Comparing the structure of glucose and 2-DG, 2-DG differs from glucose at the second carbon. Hydroxyl group of second carbon in glucose is replaced with hydrogen atomin2-DG to prevent glycolisation.[6]The hydrogen atom at second position of 2-DG can be replaced with fluorine atom to form 2-Fluro-2-Deoxy-D-Glucose to further ramp up its anti-glycolytic activity.[7]As an anti-glycolytic agent, 2-DG also plays a key role in abolishing viral replication and cytokine response by placing glycolysis as a key upstream event during SARS-CoV-2 pathogenesis.[8] As India gave nod for emergency use of 2-DG for COVID-19, official statements clarified that the drug will be available in sachets as powder to be dissolved in water likely within a month for public use. The structure of glucose and 2-DG is given in figure 1.

MECHANISM OF ACTION IN CANCER

Even though it's mechanism of action on cancer cells is not fully explained, it is hypothesised that the action of 2-DG is related to glycolysis inhibition.[9]Along with 2-DG inhibition of lipolysis also used in the treatment of cancer.[10] In some clinical studies combined use of 2-DG and metformin produces significant cell death associated with decrease in cellular Adenosine Tri Phosphate and prolonged activation of Adenosine Mono phosphate activated Protein Kinase.[11] In some studies it is found that the toxicity of 2-DG in cancer cells is due to the activity of enzymes AKR1B1 and/or AKR1B10 which is most often found in cancer cells.[12] The results of that studies shows that 2-DG destroys cancer cells in the process of being reduced by AKR1Bs, depletes their cofactor NADPH and leads to the destruction of glutathione and leads to cell death.[12] In the findings of some other studies 2-DG also stimulates the thioredoxin interacting protein (TNXIP) a tumour suppressor protein and it reduces cellular glucose uptake.[13] In another study, combination of mitochondria-targeted drugs such Mito-CP and Mito-Q with 2-DG synergises to decrease cellular ATP in two cell lines.[14]

Of all the studies, the mechanism of 2-DG is well explained in animal models and clinical trials. 2-DG is a glucose analogue and it is phosphorylated to 2-DG-P by hexokinase which cannot be metabolised furthermore but it is trapped inside the cell inhibits hexokinase, the rate limiting step of glycolysis. After inhibiting glycolysis, 2-DG interferes in various processes. At first process it stimulates energy stress by depleting intracellular ATP. Then it affects anabolic processes by reducing the production of glycolytic intermediates which are the precursors of nucleotides, lipids and proteins. At last it leads to NADPH deficiency and disrupts the antioxidant defences of cancer cells.[15]

MECHANISM OF ACTION IN COVID

Certain studies show that 2-DG has action against *Saccharomyces cerevisiae*.[16]It shows inhibitory action against the growth of microorganism and tumour cells.[17] Cells have the

ability to respond to changes in the nutrient supply in order to maintain optimal cell growth and survival. To achieve this adaptation, cell-signalling dictates alteration in the transcriptome and proteome.[18] The addition of 2-DG to the cells causes a glucose-starvation like response in the cells, which inhibits the growth and reducing viability even though glucose is present abundantly.[19] In another study 2-DG reportedly inhibits cell-wall polysaccharide biosynthesis and glycoprotein biosynthesis.[20] This causes cells to become osmotically fragile.[21] Another study shows that 2-DG attenuates inflammatory response in bacterial endothalmitis and cultured innate immune cells by inhibiting ERK signalling.[22] Another study shows 2-DG has increased viral penetration against herpes simplex virus.[23] The production of infectious herpes simplex virus was reduced to 94-98% when treated with 2-DG.[24] In another experimental study using chick embryo and yeast cells, 2-DG shows antiviral effect by inhibiting glycosylation of viral glycoproteins.[25]

Result of a study shows that, 2-DG inhibit glucose flux and oligomycin to inhibit ATP synthetase.[26]The same study shows the safety of 2-DG in SARS-CoV-2 treatment. It completely blocks viral replication in CoV-2 infected monocytes, and it also controls the CoV-2 induced increased of ACE2 and IL-1bexpression.[27] The study also shows the treatment with 2-DG inhibits CoV-2 induced TNF-α, IL-6, and IFN- α.

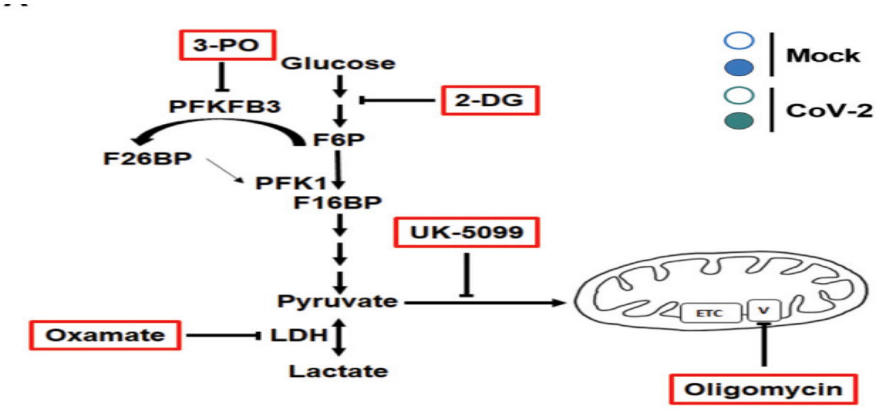

Figure.2 schematically represents the metabolism modulator action of 2-Deoxy-D-Glucose

Similarly results of another study shows that, 2-DG blocks SARS-CoV-2 replication in a colon epithelial carcinoma cell line.[28] This study shows that 2-DG abolishes viral replication and cytokine storm by compromising high energy demand and inhibiting glycolysis during SARS-CoV-2 pathogenesis. Yet another study warrants the use of 2-DG in combination with low dose radiation therapy (below 2Gy) to protect SARS-CoV-2 sensitive tissues and organs to reduce mortality and morbidity associated with COVID-19.[29]Recent in-silico study suggests that the chemical structural nature of 2-DG fits well into protease 3CLpro and also to NSP15 endoribonuclease, leading to the prevention in the binding of SARS-CoV-2 receptors to the host cells.[30] Further 2-Fluro-Deoxy-D-Glucose, an analog of 2-DG can be used as a radiotracer in the diagnosis of COVID-19 pneumonia which can minimize the radiation exposure risk of CT scan that is said to be equivalent to 300 X-rays.[31,32] The schematic representation of metabolism modulator action of 2-Deoxy-D-Glucose is given in figure 2.

DISCUSSION

CLINICAL TRIALS WITH 2-DG FOR CANCER TREATMENT

2-Deoxy-D-Glucose is not approved for the treatment of cancer till now. But it has been involved in clinical trials of various types of cancer. So far 218 trials are going on at various phases. Initial trials were conducted using intravenous form of 2-DG in leukaemia and pancreatic tumour patients.[33] Later it was discontinued due to adverse effects at high doses. BK Mohanti*et al* evaluated the toxicity and tolerance of 2-DG combined with large fraction (5 Gy) radiotherapy in postsurgical patients with supratentorial glioma.[34] Feasibility of administering the treatment (2DG + 5 Gy) is revealed by the excellent tolerance noticed in all 20 patients.

Further, the clinical examinations and magnetic resonance imaging also confirmed the absence of any brain parenchymal damage. A phase I clinical trial conducted by Mark Stein *et al* demonstrated the efficacy of 2-DG on FluroDeoxy Glucose – Positron Emission Tomography as an autophagic resistance marker in castrate resistant prostate cancer patients.[35] This study also put forth the dose of 2-DG as 45mg/kg for phase II trials. Another clinical trial conducted by L.E. Raez*et al* in twelve patients with various solid tumours revealed the safety of 2-DG.[36] In this study 2-DG is given alone and in combination with weekly docetaxel also. During Phase I/II clinical trials the combination of 2-DG+radiotherapy(γ-radiation) at an oral dose of 200 mg/kg body weight (BW), it was well tolerated in cerebral glioma patient.[37]According to the clinical studies at the higher 2-DG doses were undertaken to examine the tolerance and safety of the combined treatment in glioblastomamultiforme patients.[38]Thus combined treatment were very good upto 250mg/kg/BW, if it is more than of 300mg/kg/BW, two out of six patients cannot tolerate even vital parameters were not observed at this dose. A clinical protocol for the treatment of glioblastoma with higher doses was designed at the Kettering Medical center Kettering, Ohio, and approved by FDA, USA.

CLINICAL TRIALS WITH 2-DG FOR COVID-19 TREATMENT

India is the pioneer in using 2-DG for the treatment of COVID-19 in active corona patients. Two phases of clinical trials has completed till now. The phase II study was randomized open label multi centre active controlled trial.[39] The safety and efficacy of 2-Deoxy-D-Glucose was evaluated as an adjunctive therapy to standard of care, in comparison to standard of care alone, in the acute treatment of moderate to severe COVID -19 patients. It is a three month study conducted across various hospitals in India. The sample size for phase II trial is said to be one hundred and ten (N=110).Patients tested positive for SARS-CoV-2 by rRT-PCR on a nasophraryngeal or orophrayngeal swab were recruited as subjects.[40]The subjects were between eighteen and sixty five years of age. Each patient was administered 45mg/kg of 2-DG in morning and 18mg/kg of 2-DG in evening as powder dissolved in water for at least twenty eight days. The therapeutic range can be achieved in human plasma upon oral dosing of 63mg/kg/day. The end point is the conversion of positive r-RT-PCR into negative. The results showed that in terms of improvement of vital signs of COVID-19 symptomatic patients there was a difference of 2.5 days compared to Standard of Care (SoC). It also reduces supplemental oxygen dependence. Approval for phase III trial was granted in November 2020.This trial is going on in 27 COVID-19 hospitals spread across different states of India. Some independent experts claim the safety and efficacy data of 2-DG in phase III trial once after its approval. They expressed concern about the harm to healthy cells with high uptake of glucose like neurons due to the anti-glycolytic action of this drug. Moreover, Positron Emission Tomography with the radiotracer, 18FDG (Flurodeoxyglucose, ananalog of 2-DG) has resulted in the deposition of the radiolabel in the inflamed lungs of COVID-19patients, due to high metabolic activity induced by the corona virus infection. This phenomenon could potentially result in a preferential and disproportionately high accumulation of 2-DG in inflamed lung tissue of COVID-19 patients thereby leading to starvation in the lung cells, which in turn would lead to inhibition of viral replication.

ADVERSE DRUG REACTIONS ASSOCIATED WITH 2-DG

Apart from its therapeutic efficacy 2-DG also shows certain adverse effects in animal model studies.[41]In this study rats are treated with 1000mg/kg/day I.P for 14 days. It shows no apparent detrimental effect on spatial learning and memory which was tested by water maze experiment. At the same time 250mg/kg I.P were associated with a reversible decline in exploratory behaviour which was tested by open field measures.[42] In another animal study carcinoma rats were feeded with 2-DG.[43] It results in hyperphagic response with increased food intake, and with further increase in 2-DG it may adversely affect the body growth.[44]

As concerned with clinical trials, a study shows single intravenous doses of 2-DG up to 200mg/kg do not produce any serious adverse effects.[45] In another study significant adverse effects are identified when 2-DG is combined with doxitaxel.[46] Up to 63mg/kg common adverse effects such as fatigue, sweating, dizziness and nausea were noted. Hence 63mg/kg were selected as tolerable dose.[46]Most significant adverse effects such as reversible hyperglycemia (100%), gastrointestinal bleeding (6%), and reversible grade 3 QTc prolongation (22%) were noted.[46]

CONCLUSION

2-Deoxy-D-Glucose not widely studied and approved for the treatment of moderate and severe cases of COVID-19 in India and in contrary widely

studied and not yet approved for the treatment of cancer however plays its role as a promising candidate in both virology and oncology. This review warrants the publication of results data for phase III trials conducted using 2-DG as an adjunct in COVID-19 treatment. This article will be an eye opener for the medical field which is unambiguously struggling in the management of unabated COVID-19 pandemic. Adverse effects are inevitable in allopathic system of medicine. 2-DG also has several adverse effects. In future many trails is to be conducted to review the risk benefit ratio of 2-DG in both oncology and virology. If the results of future trials clearly indicate outweigh of benefits than risks, 2-DG will surely act as a game-changer in the field of medical science which is an ever changing subject.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

COVID-19: Corona Virus Disease 2019; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Corona Virus-2; **2-DG:** 2-Deoxy-D-Glucose; **DRDO:** Defence Research and Development Organisation; **RTPCR:** Reverse Transcription Polymerase Chain Reaction.

REFERENCES

1. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, Monneret G, Venet F, Bauer M, Brunkhorst FM, Weis S, Garcia-Salido A, Kox M, Cavaillon JM, Uhle F, Weigand MA, Flohé SB, Wiersinga WJ, Almansa R, de la Fuente A, Martin-Loeches I, Meisel C, Spinetti T, Schefold JC, Cilloniz C, Torres A, Giamarellos-Bourboulis EJ, Ferrer R, Girardis M, Cossarizza A, Netea MG, van der Poll T, Bermejo-Martín JF, Rubio I. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet RespirMed.2021; 5. doi: 10.1016/S2213-2600(21)00218-6, PMID 33965003.
2. Worldreport. 1611-1612; 397 :(10285).
3. DeSalvo J, Kuznetsov JN, Du J, Leclerc GM, Leclerc GJ, Lampidis TJ, Barredo JC. 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. doi: 10.1158/1541-7786.MCR-12-0125, PMID 22692960.
4. Aydogan B, Li J, Rajh T, Chaudhary A, Chmura SJ, Pelizzari C, Wietholt C, Kurtoglu M, and Redmond P. AuNP-DG: deoxyglucose-labeled gold nanoparticles as X-ray computed tomography contrast agents for cancer imaging. Mol Imaging Biol. 2010; 12(5):463-7. doi: 10.1007/s11307-010-0299-8, PMID 20237857.
5. 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. doi: 10.1016/j.lfs.2005.07.001, PMID 16111712.
6. Aft RL, Zhang FW, Gius D. Evaluation of 2-deoxy-D-glucose as a chemotherapeutic agent: mechanism of cell death. BrJ Cancer. 2002; 87(7):805-12. doi: 10.1038/sj.bjc.6600547, PMID 12232767.
7. Xi H, Kurtoglu M, Lampidis TJ. The wonders of 2□deoxy□d□glucose. IUBMB Life. 2014; 66(2):110-21. doi: 10.1002/iub.1251, PMID 24578297.
8. Ardestani A, Azizi Z. Targeting glucose metabolism for treatment of COVID-19. Signal Transduct TargetTher.2021; 6(1):112. doi: 10.1038/s41392-021-00532-4, PMID 33677470.
9. Zhong D, Liu X, Schafer-Hales K, Marcus AI, Khuri FR, Sun SY, Zhou W. 2-deoxyglucose induces Akt phosphorylation via a mechanism independent of LKB1/AMP-activated protein kinase signaling activation or glycolysis inhibition. MolCancerTher.2008; 7(4):809-17. doi: 10.1158/1535-7163.MCT-07-0559, PMID 18413794.
10. Kobayashi H, Nishimura H, Matsumoto K, Yoshida M. Identification of the determinants of 2-deoxyglucose sensitivity in cancer cells by shRNA library screening. BiochemBiophysResCommun. 2015; 467(1):121-7. doi: 10.1016/j.bbrc.2015.09.106, PMID 26403972.
11. Cheong JH, Park ES, Liang J, Dennison JB, savachidou D, Nguyen-Charles C, Cheng KW, Hall H, Zhang D, Lu Y, Ravoori M. Dual inhibition of tumor energy pathway by 2-deoxyglucose and metformin is effective against a broad spectrum of preclinical cancer models. *Molecular cancer therapeutics.*10 (12), 2011, 2350-2362.
12. Zhang SQ, YungKK, Chung SK, ChungSS. Aldo-keto reductases□mediated cytotoxicity of 2□deoxyglucose: A novel anticancer mechanism. Cancer Sci. 2018; 109(6):1970-80. doi: 10.1111/cas.13604, PMID 29617059.

13. Sun L, Liu X, Fu H, Zhou W, Zhong D. 2-deoxyglucose suppresses ERK phosphorylation in LKB1 and Ras wild-type non-small cell lung cancer cells. PLOSONE. 2016; 11(12):e0168793. doi: 10.1371/journal.pone.0168793, PMID 28033353.
14. 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. BiochemBiophysResCommun. 2015; 465(4):838-44. doi: 10.1016/j.bbrc.2015.08.097, PMID 26315267.
15. Cheng G, Zielonka J, Dranka BP, McAllister D, Mackinnon AC, Joseph J, Kalyanaraman B. Mitochondria-targeted drugs synergize with 2-deoxyglucose to trigger breast cancer cell death. Cancer Res. 2012; 72(10):2634-44. doi: 10.1158/0008-5472.CAN-11-3928, PMID 22431711.
16. O'Donnell AF, McCartney RR, Chandrashekarappa DG, Zhang BB, Thorner J, Schmidt MC. 2-deoxyglucose impairs Saccharomyces cerevisiae growth by stimulating Snf1-regulated and α-arrestin-mediated trafficking of hexose transporters 1 and 3. Mol CellBiol. 2015; 35(6):939-55. doi: 10.1128/MCB.01183-14, PMID 25547292.
17. Chu S, DeRisi J, Eisen M, Mulholland J, Botstein D, Brown PO, Herskowitz I. The transcriptional program of sporulation in budding yeast. Science. 1998; 282(5389):699-705. doi:10.1126/science.282.5389.699, PMID 9784122.
18. Griffin TJ, Gygi SP, Ideker T, Rist B, Eng J, Hood L, Aebersold R. Complementary profiling of gene expression at the transcriptome and proteome levels in Saccharomyces cerevisiae. Mol Cell Proteomics. 2002; 1(4):323-33. doi:10.1074/mcp.M200001-MCP200, PMID 12096114.
19. Jaspers HT, van Steveninck J. Transport-associated phosphorylation of 2-deoxy-d-glucose in Saccharomyces fragilis. BiochimBiophysActa. 1975; 406(3):370-85. doi:10.1016/0005-2736(75)90017-6, PMID 1182170.
20. Lobo Z, Maitra PK. Resistance to 2-deoxyglucose in yeast: a direct selection of mutants lacking glucose-phosphorylating enzymes. Mol Gen Genet. 1977; 157(3):297-300. doi:10.1007/BF00268666, PMID 340926.
21. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene. 2006; 25(34):4633-46. doi:10.1038/sj.onc.1209597, PMID 16892078.
22. Francis R, Singh PK, Singh S, Giri S, Kumar A. Glycolytic inhibitor 2-deoxyglucose suppresses inflammatory response in innate immune cells and experimental staphylococcal endophthalmitis. ExpEyeRes.2020; 197:108079. doi: 10.1016/j.exer.2020.108079.
23. 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. doi: 10.1016/0042-6822(82)90300-2, PMID 6293188.
24. McDowell W, Datema R, Romero PA, Schwarz RT. Mechanism of inhibition of protein glycosylation by the antiviral sugar analogue2-deoxy-2-fluoro-D-mannose: inhibition of synthesis of Man (GlcNAc) 2-PP-Dol by the guanosine diphosphate ester. Biochemistry. 1985; 24(27):8145-52. doi: 10.1021/bi00348a046, PMID 4092061.
25. Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoff JS, Carregari VC, de Biagi Junior CAO, Crunfli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira FB, Velloso LA, Vinolo MAR, Damasio A, Proença-Módena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM. 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. doi: 10.1016/j.cmet.2020.07.007, PMID 32697943.
26. BojkovaD, KlannK, KochB, WideraM, KrauseD, CiesekS, CinatlJ, MunchC2020. Proteomics of SARS-CoV-2-infected host cells reveals €therapy targets. Nature. Published online May14, 2020.
27. BojkovaD, Klann K, Koch B, Widera M, Krause D, Ciesek S, Cinatl J, Münch C. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature.2020; 583(7816):469-72. doi: 10.1038/s41586-020-2332-7, PMID 32408336.
28. Ardestani A, Azizi Z. Targeting glucose metabolism for treatment of COVID-19. Signal Transduct TargetTher.2021; 6(1):112. doi: 10.1038/s41392-021-00532-4, PMID 33677470.
29. Verma A, Adhikary A, Woloschak G, Dwarakanath BS, PapineniRVL. A combinatorial approach of a polypharmacological adjuvant 2-deoxy-D-glucose with low dose radiation therapy to quell the cytokine storm in COVID-19 management. IntJ RadiatBiol. 2020; 96(11):1323-8. doi: 10.1080/09553002.2020.1818865, PMID 32910699.

30. Balkrishna A, Thakur P, Singh S, Dev S, Jain V, Varshney A, Sharma R. Glucose antimetabolite 2-deoxy-D-glucose and its derivative as promising candidates for tackling COVID-19: insights derived from in silico docking and molecular simulations. AuthoreaPrepr. 2020.
31. O'Neill H, Doran S, Fraioli F, Nasoodi A. A twisted tale-radiological imaging features of COVID-19 on 18 F-FDG PET/CT. EurJ Hybrid Imaging. 2020; 4(1):1.
32. WangYXJ, Liu WH, Yang M, Chen W. The role of CT for Covid-19 patient's management remains poorly defined. Ann TranslMed. 2020; 8(4):145. doi: 10.21037/atm.2020.02.71, PMID 32175437.
33. Dwarakanath BS, Jain V. Targeting glucose metabolism with 2-deoxy-D-glucose for improving cancer therapy. Future Oncol.2009; 8(4):581-5.
34. Mohanti BK, Rath GK, Anantha N, Kannan V, Das BS, Chandramouli BA, Banerjee AK, Das S, Jena A, Ravichandran R, Sahi UP, Kumar R, Kapoor N, Kalia VK, Dwarakanath BS, Jain V. Improving cancer radiotherapy with 2-deoxy-D-glucose: phase I/II clinical trials on human cerebral gliomas. IntJ RadiatOncol Biol Phys* *Biology* Physics*. 1996; 35(1):103-11. doi: 10.1016/s0360-3016(96)85017-6, PMID 8641905.
35. Stein M, Lin H, Jeyamohan C, Dvorzhinski D, Gounder M, Bray K, Eddy S, Goodin S, White E, DiPaola RS. Targeting tumor metabolism with 2□deoxyglucose in patients with castrate□resistant prostate cancer and advanced malignancies. Prostate. 2010; 70(13):1388-94. doi: 10.1002/pros.21172, PMID 20687211.
36. Raez LE, Rosenblatt J, Schlesselman J, Langmuir V, Tidmarsh G, Rocha-Lima C, Papadopoulos K, O'Connor J, Baldie P, Lampidis T. Combining glycolytic inhibitors with chemotherapy: phase I trial of 2-deoxyglucose and docetaxel in patients with solid tumors. J ClinOncol. 2005; 23(16_suppl):3190. doi: 10.1200/jco.2005.23.16_suppl.3190.
37. Singh D, Banerji AK, Dwarakanath BS, Tripathi RP, Gupta JP, Mathew TL, Ravindranath T, Jain V. Optimizing cancer radiotherapy with 2-deoxy-D-glucose dose escalation studies in patients with glioblastoma multiforme. StrahlentherOnkol. 2005; 181(8):507-14. doi: 10.1007/s00066-005-1320-z, PMID 16044218.
38. Dwarakanath BS, Singh D, Banerji AK, Sarin R, Venkataramana NK, Jalali R, Vishwanath PN, Mohanti BK, Tripathi RP, Kalia VK, Jain V. Clinical studies for improving radiotherapy with 2-deoxy-D-glucose: present status and future prospects. J CancerRes Ther. 2009; 5(9); Suppl 1:S21-6. doi: 10.4103/0973-1482.55136, PMID 20009289.
39. Clinical trialsregistry. India [citedMay10, 2021]. Available from:http://www.ctri.nic.in/Clinicaltrials/login.php.
40. RaoMVV, Juneja A, Maulik M, Adhikari T, Sharma S, Gupta J, Panchal Y, Yadav N. Emerging trends from COVID-19 research registered in the Clinical Trials Registry-India. Indian J MedRes. 2021; 153(1 & 2):26-63. doi: 10.4103/ijmr.IJMR_2556_20, PMID 33818466.
41. Ockuly JC, Gielissen JM, Levenick CV, Zeal C, Groble K, Munsey K, Sutula TP, Stafstrom CE. Behavioral, cognitive, and safety profile of 2-deoxy-2-glucose (2DG) in adult rats. *Epilepsy research*. 101(3), 2012, 246-252.
42. Stafstrom CE, Ockuly JC, Murphree L, Valley MT, Roopra A, Sutula TP. Anticonvulsant and antiepileptic actions of2-deoxy-D-glucose in epilepsy models. AnnNeurol.2009; 65(4):435-47. doi: 10.1002/ana.21603, PMID 19399874.
43. Singh S, Pandey S, Bhatt AN, Chaudhary R, Bhuria V, Kalra N, Soni R, Roy BG, Saluja D, Dwarakanath BS. Chronic dietary administration of the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) inhibits the growth of implanted Ehrlich's ascites tumor in mice. PLOSONE. 2015; 10(7):e0132089. doi: 10.1371/journal.pone.0132089, PMID 26135741.
44. Zhu Z, Jiang W, McGinley JN, Thompson HJ. 2-deoxyglucose as an energy restriction mimetic agent: effects on mammary carcinogenesis and on mammary tumor cell growth in vitro. Cancer Res. 2005;65(15):7023-30. doi: 10.1158/0008-5472.CAN-05-0453, PMID 16061689.
45. Catena R, Bottoni P, Pontoglio A, Mastrototaro L, Giardina B. Glycolytic enzyme inhibitors in cancer treatment. Expert OpinInvestigDrugs. 2008;17(10):1533-45. doi: 10.1517/13543784.17.10.1533, PMID 18808312.
46. Raez LE, Papadopoulos K, Ricart AD, Chiorean EG, DiPaola RS, Stein MN, Rocha Lima CM, Schlesselman JJ, Tolba K, Langmuir VK, Kroll S, Jung DT, Kurtoglu M, Rosenblatt J, Lampidis TJ. A phase I dose-escalation 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. doi: 10.1007/s00280-012-2045-1, PMID 23228990.