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2-Deoxy D-Glucose in COVID-19: Current Research Trends

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ABSTRACT

2-Deoxy D- glucose is a novel drug. It is an analogue of glucose which has innate therapeutic uses due to both its antiviral properties as well as its anti-neoplastic action. The SARS-CoV-2 virus binds to the host cell via the (S2) spike glycoprotein. Once viral entry has been gained into the host cell the virus hijacks the host's intracellular machinery via 2 factors; 3CLpro and NSP15. It has been shown through the use of Toxicity estimation software as well as via Molinspiration that 2-Deoxy D- glucose and its aforementioned isomers can effectively bind with 3CLpro and NSP15 and intern thus immobilize the SARS-CoV-2 virus via the incapacitation of its viral receptors. On a molecular level the 2-Deoxy D- glucose derivatives produce a H bond with the glutamine AA residues of the SARS-CoV-2 (S2) spike, as well form a Hydrogen bond with the 2 Deoxy D- glucose and proline residues of the SARS-CoV-2 protease. It is thus evident via both molecular and in silico studies that 2 Deoxy D- glucose and its isomers have the ability to offer further protection and or have imperative diminution capabilities in the treatment of patients with the COVID-19 infection. 2-Deoxy D- glucose has shown promising results in clinical trials and has produced faster recovery in hospitalized patients and abridged additional oxygen dependence in COVID-19 patients in various states across India. The scope and potential for the use of 2-Deoxy D- glucose in the treatment of COVID-19 is evident. It is therefore of great importance that further in vivo studies are conducted with 2-Deoxy D-glucose in order to expedite the process of bringing this potentially lifesaving drug to market.

Keywords: Coronavirus infections; COVID-19 drug treatment; drug development; pharmacology; therapeutics; SARS-CoV-2.

INTRODUCTION

The coronavirus pandemic has globally, as of the 31st of May 2021 infected 170, 051, 718 individuals and has claimed 3, 540, 437 lives. Multiple countries are experiencing their third and fourth waves with dire consequences due to the great morbidity and mortality which is associated with the SARS-CoV-2 infections.[1]

The severity and widespread impact of this

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infection coupled with its novelty has meant that no full proof, specific drug is available for the treatment of patients. This innate dearth in the pharmacological treatment of patients has led to the development and or the trials of a wide variety of drugs for the treatment of COVID-19. One such novel drugs which is making headway is 2-Deoxy D- glucose. [2,3]

2-Deoxy D- glucose:

2-Deoxy D- glucose is a novel drug. It is an analogue of glucose which has innate therapeutic uses due to both its antiviral properties as well as its anti-neoplastic action. 2-Deoxy D- glucose has traditionally been used in radio-imaging as a diagnostic drug; it has found a particular niche in PET (positron emission tomography) scans which are used to isolate glucose hunger in various neoplastic conditions.[2]

Molecular makeup of 2 Deoxy D- glucose:

2-Deoxy D- glucose is a molecularly altered version of traditional glucose. In particular the functional group at the second carbon atom has been altered. The molecule has an H atom within the carbon atom in position C-2 as opposed to the traditional hydroxyl group. The 2- Deoxy D- glucose molecule therefore contains four hydroxyl groups as opposed to its traditional counterpart (D-glucose) which contains five hydroxyl groups.[2,4]

Mechanism of 2-Deoxy D- glucose:

2-Deoxy D- glucose gains entry into the cell via the same mechanism a traditional glucose molecule would; via GLUT transporters. Once it has entered into the cell and is within the cytoplasm the enzyme hexokinase initiates the phosphorylation process. The alteration of the glucose molecule thus leads to 2-deoxy-D-glucose-6-phosphate not being able to be metabolized further. This barrier and break in the metabolic pathway of 2-Deoxy D-glucose causes the accumulation of 2-deoxy-D-glucose-6-phosphate within the cell and this intern retards the production of ATP and thus leads to a deficit in energy. [5,6]

Uses of 2-Deoxy D- glucose :

2-Deoxy D- glucose has a wide array of functions and practical applications spanning from the fields of oncology, virology all the way to neurology. 2-Deoxy D- glucose has been a mainstay drug used in both the diagnostic and therapeutic realm in respect to cancer screening and treatment. In cancer screening and treatment 2-Deoxy D- glucose utilizes the universal traits of neoplasia to upregulate both the utilization and uptake of glucose. [7,8]

In screening, the principle of the Warburg effect is applied via PET (positron emission tomography) scans. The Warburg effect is a phenomenon whereby cancer cells revert and switch over to the unconventional anaerobic glycolysis pathway to form adenosine triphosphate; this mechanism and pathway of adenosine triphosphate production is less efficient and yields a lower amount of ATP as opposed to the conventional mitochondrial oxidation pathway utilized by normal cells. This procedure capitalizes on the basic pathological principle of the "hallmarks of neoplasia." The PET (positron emission tomography) scan is used by oncologists to identify cancers on the basis of "glucose hunger." The procedure is simple and consists of fluorescein tagged 2-Deoxy D- glucose which is infused into a patient whilst undergoing a CT scan, dually regions which utilize more glucose are brighter and correspond to the possible neoplasm. The use of PET scans in the diagnosis of cancer is now unrefuted and its application therein is invaluable. [7,8,9]

A study conducted by Singh D, et al. on 2-Deoxy

D- glucose, depicts the permissive action of 2-Deoxy D- glucose in the treatment of cancers. It is stipulated that 2-Deoxy D- glucose has the potential to increase and amplify the efficacy of radiotherapy, specifically in glioblastoma multiforme patients. [10]

2-Deoxy D- glucose has been found to be an effective suppressant of seizures via modulating the glycolytic metabolic pathway which stimulates and causes neuronal excitability. The antiseizure effect of 2-Deoxy D- glucose has been observed in animal studies, where it provided seizure protection in 75% of the rats being studied. [11]

It has been proven that 2-Deoxy D- glucose has antiviral properties so as to the degree that the production of the herpes simples 1 virus (HSV1) was decreased by 94-98%. It is thus, this antiviral property which is being exploited for the treatment of COVID-19. [12]

2-Deoxy D- glucose in COVID-19:

2-Deoxy D- glucose and a host of its derivatives and isomers namely 1,3,4, 6 tetra O acetyl 2 deoxy D-glucopyranose have been tested and studied via the use of ligand-receptor docking and binding. The relative assessments of the receptor and binding interactions have been scored via molecular dynamic analysis. The SARS-CoV-2 virus binds to the host cell via the (S2) spike glycoprotein. Once viral entry has been gained into the host cell the virus hijacks the host's intracellular machinery via 2 factors; 3CLpro (viral main protease) and NSP15 (endoribonuclease).[2,13]

It has been shown through the use of Toxicity estimation software as well as via Molinspiration that 2-Deoxy D- glucose and its aforementioned isomers can effectively bind with 3CLpro (viral main protease) and NSP15 (endoribonuclease) and intern thus immobilize the SARS-CoV-2 virus via the incapacitation of its viral receptors. On a molecular level the 2-Deoxy D- glucose derivatives produce a H bond with the glutamine AA residues of the SARS-CoV-2 (S2) spike, as well form a Hydrogen bond with the 2 Deoxy D- glucose and proline residues of the SARS-CoV-2 protease. It is thus evident via both molecular and in silico studies that 2 Deoxy D- glucose and its isomers have the ability to offer further protection and or have imperative diminution capabilities in the treatment of patients with the COVID-19 infection.[2, 13]

Invitro cell culture experiments performed in Hyderabad have further supported the notion that the use of 2-Deoxy D- glucose is warranted as an effective therapeutic tool in COVID-19 patients. Various cell cultures of the SARS-CoV-2 virus performed both in the presence and the absence of 2-Deoxy D- glucose have depicted those thicker viral plaques and growth are present in the absence of 2-Deoxy D- glucose as opposed to when it is present.[2,14]

2-Deoxy D- glucose has shown promising results in clinical trials and has produced faster recovery in hospitalized patients and abridged additional oxygen dependence in COVID-19 patients in various states across India[14].

CONCLUSIONS

The scope and potential for the use of 2-Deoxy D- glucose in the treatment of COVID-19 is evident. The accessibility and ease of use of such a drug will be both an imperative and instrumental tool in the war against COVID-19. It is therefore of great importance that further in vivo studies are conducted with 2-Deoxy D- glucose in order to expedite the process of bringing this potentially lifesaving drug to market.

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