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The structure of the membrane protein of SARS-CoV-2 resembles the sugar transporter semiSWEET

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the disease COVID-19 that has decimated the health and economy of our planet. The virus causes the disease not only in people but also in companion and wild animals. People with diabetes are at risk of the disease. As yet we do not know why the virus is highly successful in causing the pandemic within 3 months of its first report. The structural proteins of SARS include, membrane glycoprotein (M), envelope protein (E), nucleocapsid protein (N) and the spike protein (S). The structure and function of the most abundant structural protein of SARS-CoV-2, the membrane (M) glycoprotein is not fully understood. Using *in silico* analyses we determined the structure and potential function of the M protein. The M protein of SARS-CoV-2 is 98.6% similar to the M protein of bat SARS-CoV, maintains 98.2% homology with pangolin SARS-CoV, and has 90% homology with M protein of SARS-CoV; whereas, the similarity was only 38% with the M protein of MERS-CoV. *In silico* analyses showed that the M protein of SARS-CoV-2 has a triple helix bundle, form a single 3-transmembrane domain (TM), and are homologous to the prokaryotic sugar transport protein semiSWEET. SemiSWEETs are related to the PQ-loop family that function as cargo receptors in vesicle transport, mediates movement of basic amino acids across lysosomal membranes, and is also involved in phospholipase flippase function. The advantage and role of sugar transporter-like structure in viruses is unknown. Endocytosis is critical for the internalization and maturation of RNA viruses, including SARS-CoV-2. Sucrose is involved in endosome and lysosome maturation and may also induce autophagy, pathways that help in the entry of the virus. It could be hypothesized that the semiSWEET sugar transporters could be used in multiple pathways that may aid in the rapid proliferation and replication of the virus. Biological experiments would validate the presence and function of the semiSWEET sugar transporter.

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Key words

SARS-CoV-2, COVID-19, Coronavirus, Virus, sugar transporter, SemiSWEET, Membrane glycoprotein.

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Introduction

The coronavirus disease 2019 (COVID-19) is currently responsible for the pandemic that has decimated the health and economy of every country. COVID-19 is regarded as a respiratory disease that manifests with fever, cough, shortness of breath or difficulty breathing, chills, muscle pain, headache, sore throat, loss of taste and smell. Other symptoms include diarrhea, nausea and vomiting (Yang et al. 2020; Effenberger et al. 2020). Many patients with the COVID-19 are asymptomatic, but are able to transmit the virus to others (Bai et al. 2020; Gao et al. 2020). The prolonged pandemic has resulted in social distancing, travel restrictions, decreased trade, high unemployment, commodity price decline, and financial stress that has impacted the global economy. COVID-19 disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the betacoronavirus genus (Wang et al. 2020). The disease has resulted in a mortality of 0.5-8.0 percent. The death rate has varied with time. As yet, there are no effective drugs available for treatment of the disease nor vaccines available commercially to protect against the virus.

The major structural proteins of SARS-CoV-2 are spike (S), membrane (M), envelop (E), and the nucleocapsid (N) proteins (Shereen et al. 2020; Chan et al. 2020). The spike protein of SARS-CoV-2 uses the host angiotensin-converting enzyme 2 (ACE2) as the entry receptor (Wrapp et al. 2020). Hence, the research community has an interest in studying the spike protein for drug and vaccine development.

The most abundant structural protein of coronaviruses is the M glycoprotein; it spans the membrane bilayer, leaving a short NH2-terminal domain outside the virus and a long COOH terminus (cytoplasmic domain) inside the virion (Mousavizadeh and Ghasemi, 2020). The M protein can bind to all other structural proteins. Binding with M protein helps to stabilize N proteins and promotes completion of viral assembly by stabilizing N protein-RNA complex, inside the internal virion (Astuti and Ysrafil, 2020). As the M proteins cooperates with the S protein, mutations may influence host cell attachment and entry of the viruses (Bianchi et al. 2020). The function of the M protein is also not fully understood.

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Sugars will eventually be exported transporters (SWEETs) and SemiSWEETs are sugar transporters in eukaryotes and prokaryotes, respectively. SWEET proteins were first identified in plants as the novel family of sugar transporters that mediates the translocation of sugars across cell membranes (Chen et al. 2010, Feng and Frommer, 2015; Jia et al. 2018; Jeena et al. 2019). Sugar transporters are essential for the maintenance of blood glucose levels in animals, nectar production, phloem loading, seed and pollen development in plants, and also in pathogen nutrition (Chen et al. 2010; Jeena et al. 2019). Engineering of SWEET mutants using genomic editing tools mediated resistance to pathogens (Chen, 2014).

In eukaryotes, SWEET can discriminate and transport the uptake of mono and disaccharides across the plasma membrane by allowing solutes to permeate across biological membranes following a concentration gradient (Chen et al. 2010; Chen, 2014; Han et al. 2017). Eukaryotic SWEETs are composed of seven transmembrane helices (TMHs) that contain a pair of three transmembrane repeats, which are connected by an additional helix, while SemiSWEETs, the homologs of SWEETs in prokaryotes, contain three TMHs (Xuan et al. 2013; Feng and Frommer, 2015). The human genome contains only one *SWEET* gene and may be involved in glucose transport (Chen et al. 2010).

The prokaryotic semiSWEETs may be involved in the metabolism and transport of sugar synthesis. The semiSWEETs of prokaryotes are more diverse than SWEETs in plants; they seldom have homologs sharing >50% identity (Jia et al. 2018). The limited number of semiSWEET homologs suggest that they are not as important as the SWEETs in eukaryotes (Jia et al. 2018).

It is clearly not understood the function and role of the M proteins of the SARS-CoV-2 during host infection. Here, we report that the M proteins of SARS-CoV-2 are structurally similar to semiSWEET sugar transport proteins of prokaryotes based on *in silico* analyses.

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Materials and Methods

SARS-CoV-2 protein structure

The structural protein sequences of the SARS-CoV-2 were downloaded from Pubmed (https://www.ncbi.nlm.nih.gov/pubmed), protein database. The structural proteins include Membrane protein (Accession No. QJA17755), Envelope protein (Accession No. QJA17754), Spike protein (Accession No. QHR63290), Nucleocapsid protein (Accession No. QJC20758).

Protein modeling

Three-dimensional structures of proteins provide valuable insights into their function on a molecular level and inform a broad spectrum of applications in life science research. A detailed description of the interactions of proteins and the overall quaternary structure is essential for a comprehensive understanding of biological systems, how protein complexes and networks operate and how it could be modulated. Swiss model is a server that is used for 3D structure prediction. SWISS-MODEL is the first fully automated protein homology modelling server and is being updated continuously (Waterhouse et al. 2018). In our study, homology modeling was constructed using Swiss model server (http//swissmodel.expasy.org/) with default settings. The M protein sequence of SARS-CoV-2 was entered in FASTA format.

Residue-based diagram of proteins, also called snake diagrams or protein plots, are 2D representations of a protein sequence that contains information about properties such as secondary structure (Skrabanek et al. 2003). To determine snake diagram model of protein we used Protter (http://wlab.ethz.ch/protter). Protter is an interactive and customizable web-based application that enables the integration and visualization of both annotated and predicted protein sequence features together with experimental proteomic evidence for peptides and posttranslational modifications, onto the transmembrane topology of a protein. It allows users to choose from numerous annotation sources,

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integrate own proteomics data files, select best-suited peptides for targeted quantitative proteomics applications and export publication-quality illustrations (Omasits et al. 2014).

Sequence alignment

Multiple sequence alignments (MSAs) are essential in most bioinformatics analyses that involve comparing homologous sequences (Thompson et al. 1994). ClustalW2 is a server for MSA that is also used for phylogenetic tree analysis. Multiple sequence alignment between M protein of SARS-CoV-2 and the M proteins of SARS-CoV, bat SARS-CoV, pangolin SARS-CoV, and MERS-CoV as well as semiSWEET sequences from different microorganisms was performed using the clustalW2 server (http:/www.ebi.ac.uk/tools/msa/clustalW2/).

Results

The S protein of SARS-CoV-2 binds to ACE2 receptors of the host for cell entry and may be a key target for drugs and vaccines. Hence, the S protein of SARS-CoV-2 virus is well characterized. The SARS-CoV-2 is one of the most successful virus as it caused a pandemic within just three months of its first report in Wuhan, China. As yet, we do not yet know why the virus is successful in inducing a pandemic leading to millions of infection and thousands of death.

Three-dimensional (3D) protein structures provide valuable insights into the molecular basis of protein function (Schweede et al. 2003). Using *in silico* techniques the structure and potential function of the M protein of the SARS-CoV-2 virus is elucidated.

The structural protein sequence of the membrane protein (M) of SARS-CoV-2 is shown in Fig. 1. The FASTA sequence of the M protein was entered into the SWISS-MODEL server. Based on the sequence, the structure of the molecule was predicted as

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bidirectional sugar transporter SWEET2b. The ribbon representation, spacefill and surface models of the M protein is shown in Fig. 2.

The sugar transporter SWEET of eukaryotes are generally composed of seven transmembrane helices. Modeling proteins using residue-based diagram (snake diagrams) helps understand its function. Hence, we used Protter to model the M protein.

The M glycoprotein is the most abundant envelope protein of SARS-CoV-2. *In silico* analyses of the M protein of SARS-CoV-2 using Protter demonstrated that it has a triple helix bundle, and formed a single 3-transmembrane domain (TM). In addition, the M glycoprotein has a short amino terminal outside the membrane and a long carboxy-terminal domain inside the membrane (Fig. 3A). The SWISS-MODEL predicted the M glycoprotein as SWEET2b. However, the M protein only has three transmembrane helices, not six or seven transmembrane helices observed in the SWEET sugar transporters of eukaryotes. Hence, the M glycoprotein structure of SARS-CoV-2 may be considered as semiSWEET. To confirm accuracy of the study, we also modeled the E, N and S proteins of SARS-CoV-2. The modeling showed that the E protein has long outer amino terminal, a single helix and a short inner carboxy-terminal (Fig. 3B). The N protein had its entire structure inside the membrane (Fig. 3C). Whereas, the S protein had the majority of its structure outside the membrane with only a short carboxy-terminal inside the membrane (Fig. 3D).

ClustalW2 was used to determine homology between M proteins of different coronaviruses. SARS-CoV-2 M protein has a sequence similarity of 98.6% with the M protein of bat SARS-CoV, 98.2% homology with the pangolin SARS-CoV, 89.14% similarity with the M protein of SARS-CoV and a sequence similarity of 38.36% with the M protein of MERS-CoV (Fig. 4A-D). The MERS-CoV M protein had more homology with the sugar transporter SWEET (Table 1).

The SemiSWEET sugar transporter of prokaryotes are more diverse than SWEET counterpart in plants. In the prokaryotes the semiSWEET seldom share identity. We used

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ClustalW2 to determine sequence homology of the sugar transporters of multiple microorganisms. The sequence of semiSWEET of the M glycoprotein of SARS-CoV-2 had a similarity of 26% with the semiSWEET of *Rhizobiales* and 20% with *Streptococcus pneumoniae* demonstrating that the semiSWEET of the SARS-CoV-2 may be highly conserved (Fig. 5A, B).

Discussion

The COVID-19 pandemic caused by the coronavirus SARS-CoV-2 is spreading at an alarming rate and has resulted in an unprecedented health emergency all over the world (Ghosh et al. 2020). The rapid spread of SARS-CoV-2 justifies the global effort to identify effective preventive strategies and optimal medical management (Castagnoli et al. 2020).

As yet there are no effective vaccines to protect against COVID-19 nor effective approved drugs to treat patients with the disease. The development of antivirals is an urgent priority to combat the disease (Ghosh et al. 2020). In the absence of effective and safe vaccines or antivirals to control the disease, strategies for mitigating the burden of the pandemic is focused on non-pharmaceutical interventions, such as social-distancing, contact-tracing, quarantine, isolation, and the use of face-masks in public (Ngonghala et al. 2020).

The primary route of transmission of COVID-19 is likely via respiratory droplets and is known to be transmissible from pre-symptomatic and asymptomatic individuals (Howard et al. 2020). Infected people spread viral particles during talking, breathing, coughing, or sneezing. Such viral particles are known to be encapsulated in globs of mucus, saliva, and water, and the fate/behavior of globs in the environment depends on the size of the globs (Jayaweera et al. 2020). Studies show that SARS-CoV-2 can be detected in the air and remain viable 3 hours after aerosolization. The weight of combined evidence supports airborne precautions for the occupational health and safety of health workers treating patients with COVID-19 (Bahl et al. 2020).

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It has been shown that wearing mask reduces the transmissibility per contact by reducing transmission of infected droplets in both laboratory and clinical contexts. Public mask wearing is most effective at reducing spread of the virus when compliance is high. The decreased transmissibility could substantially reduce the death toll and economic impact while the cost of the intervention is low (Howard et al. 2020). The community-wide benefits are likely to be greatest when face masks are used in conjunction with other non-pharmaceutical practices such as social-distancing, and when adoption is nearly universal (nation-wide) and compliance is high (Eikenberry et al. 2020). Chu et al. (2020) support physical distancing of 1 m or more and hypothesized that contact tracing could reduce the disease transmission.

Understanding the biochemical events of the coronavirus replication cycle may provide a number of attractive targets for drug development (Ghosh et al. 2020). Current strategies involve developing drug and vaccine candidates against spike (S) protein of the virus. The rationale being that neutralizing antibodies against the S protein prevent uptake of the virus via the human ACE2 receptor (Le et al. 2020). Identifying drug targets that blunt the activity of the virus may lead to effective treatments for COVID-19.

Viruses are non-living entities, without any organelles devoid of their own metabolism, though they have the capability to dramatically modify the host cellular metabolism upon entry. Viruses upregulate consumption of glucose and converge on similar metabolic pathways for anabolism (Thaker et al. 2019). Virus-induced metabolism may provide free nucleotides for rapid viral genome replication, increased amino acid production for rapid virion assembly, and high amounts of ATP for the high energy costs of genome replication and packaging. The mechanism for increased glucose uptake by the virus is still not clearly understood.

Glucose is the energy source of cells and tissues. Cellular uptake of glucose is a fundamental process for metabolism, growth, and homeostasis. Glucose is a polar molecule that does not readily diffuse across the hydrophobic plasma membrane of the cells. Glucose molecules are transported through the glucose transporters that include,

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GLUTs, the sodium-driven glucose symporters SGLTs, STP, and SWEETs (Deng and Yan, 2016). SWEETs are seen in plants and animals. SWEET induction by plant pathogens leads to secretion of sucrose that is used by these microorganisms for nutrition/reproduction (Bezrutczyk et al. 2017).

The bacterial ancestors of SWEET, known as semiSWEET are the smallest of the sugar transporters and assemble into dimers (Xuan et al. 2013; Chen et al. 2015; Lee et al. 2015). In fact, eukaryotic SWEETs consist of two SemiSWEET-like units fused via an inversion linker transmembrane helix (Jia et al. 2018). The diverse gene neighbors of semiSWEETs suggest that semiSWEETs may transport diverse substrates and play several physiological roles in different organisms (Jia et al. 2018). The SWEETs and their bacterial homologues, SemiSWEETs, are related to the PQ-loop family, characterized by highly conserved proline and glutamine residues (PQ-loop motif) (Lee et al. 2015). The PQ-loop family exhibits diverse activities; they function as cargo receptors in vesicle transport, mediates movement of basic amino acids across lysosomal membranes, and is also involved in phospholipase flippase function (Saudek, 2012; Yamamoto et al. 2017; Kawano-Kawada et al. 2019). As yet there are no reports of sugar transporters in viruses.

It is not known how SARS-CoV-2 has been successful to spread all over the world within three months of its first report in Wuhan, China. Identifying the mechanisms of how viruses alter cellular metabolism and where in the virus life cycle these metabolic changes are necessary will provide an understanding of virus replication needs and potentially provide cellular targets for inhibition of these viruses. In this paper using *in silico* data analysis we demonstrate that the structure of the membrane (M) glycoprotein of SARS-CoV-2 resemble the semiSWEET sugar transporter of the prokaryotes.

Clues to the viral metabolism can be understood from the patient population at risk of infection. It is known that people with diabetes are more prone to COVID-19 disease (Bornstein et al. 2020). Recent reports indicate that the SARS-CoV-2 induces diabetes in non-diabetic people (Iocobellis et al. 2020). A large case study of COVID-19 patients

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reported that diabetic subjects had a threefold higher mortality rate than did those without diabetes (7.3% vs 2.3%) (Wu and McGoogan, 2020).

Diabetes is a risk factor as well as prevalent in patients infected with other coronaviruses, including SARS-COV (Yang et al. 2010) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) (Badawi and Ryoo, 2016; Nassar et al. 2018). It has been demonstrated that SARS coronavirus enters islets and damages islets causing acute diabetes (Yang et al. 2010). As people with diabetes have high glucose, the environment may favor proliferation of viruses. MERS-CoV utilizes dipeptidyl peptidase 4 (DPP4), and modeling of the structure of SARS-CoV-2 spike glycoprotein predicts that it can interact with human DPP4 in addition to ACE2. DPP4 is a ubiquitous membrane-bound aminopeptidase that circulates in plasma; it is multifunctional with roles in nutrition, metabolism, and immune and endocrine systems. DPP4 activity differentially regulates glucose homeostasis and inflammation via its enzymatic activity and nonenzymatic immunomodulatory effects. DPP4 inhibitors, or gliptins is approved for the treatment of type 2 diabetes mellitus (Bassendine et al. 2020). Rhee et al. (2020) reported that DPP-4 inhibitor is significantly associated with a better clinical outcome of patients with COVID-19.

Virus uses multiple mechanisms for the uptake of glucose. *Human cytomegalovirus* (HCMV), a herpesvirus, induces the sugar transporter, GLUT4 to increase glucose uptake during infection (Yu et al. 2011). Whereas, transmissible gastroenteritis virus (TGEV), a coronavirus induces multiple sugar transporters EGFR, SGLT1 and GLUT2 for glucose uptake (Dai et al. 2016). Rhinoviruses (RVs) are responsible for the majority of upper airway infections and they enhance the expression of the PI3K-regulated glucose transporter GLUT1; glucose deprivation from medium and via glycolysis inhibition by 2-deoxyglucose (2-DG) impairs viral replication (Gualdoni et al. 2018).

Sucrose is used for energy metabolism by cells. In addition, sucrose is also used for endosome and lysosome maturation, autophagosomes and also to induce autophagy (Hu

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et al. 2015; Higuchi et al. 2015; Yang and Shen, 2020). Coronaviruses, including SARS, SARS-CoV-2 use endosome for cellular entry, and they are known to manipulate autophagosome and autolysosome for viral dissemination in the cell (Burkard et al. 2014; Yang and Shen, 2020).

The membrane (M) glycoprotein is the most abundant envelope protein of coronaviruses (deHaan et al. 1999). *In silico* analysis demonstrated that M protein of SARS-CoV-2 is 98.6% similar to the M protein of bat SARS-CoV, maintains 98.2% homology with pangolin SARS-CoV, and 90% homology with M protein of SARS-CoV; whereas, the similarity was only 38% with M protein of MERS-CoV. Thus, the M protein of SARS-CoV-2 resembles M protein of bat and pangolin SARS-CoV compared to MERS-CoV. A recent paper by Zhang et al. (2020) reported that at the genomic level SARS-CoV- 2 is 96.2% identical to bat-SARS-CoV (RaTG13) and 91.02% identical to pangolin SARS-Co-V.

In silico analysis showed that the M protein of SARS-CoV-2 resembles the sugar transporter, SWEET. Upon analysis, it was observed that other coronaviruses including SARS-CoV, bat SARS-CoV, pangolin SARS-CoV and MERS-CoV has M proteins homologous to the sugar transporter SWEET. Further analysis by residue-based structure demonstrated that the protein has the characteristic structure of semiSWEET, the sugar transporter of prokaryotes. To our knowledge this is the first report of the presence of a sugar transporter in a virus membrane. It is known that the prokaryotes have diverse sugar transporters. In our analysis, the SARS-CoV-2 sequence of semiSWEET has no homology to other prokaryotes.

An advantage of the virus having a sugar transporter in its membrane is that it may influence energy metabolism. How, the virus utilizes sugar molecules is unknown. In addition, it could be hypothesized that the sucrose transporters of the virus membrane may influence sucrose entry into the endosome, lysosome or autophagosome that are manipulated by the virus, thereby aiding the virus release into cells. Thus, the presence of a semiSWEET glucose transporter in the M protein of the virus may be an efficient mechanism that may induce its rapid proliferation.

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Generally, the enveloped viruses, including SARS-CoV-2, use a two-step procedure to release their genetic material into the cell. 1) They bind to specific surface receptors of the target cell membrane, and 2) they fuse the viral and cell membranes. This second step may occur at the cell surface or after internalization of the virus particle by endocytosis. Currently, it is not known how the M proteins of the virus is fused to the host cell membrane. If the M proteins are fused to host cell membrane, it could theoretically function as a sugar transporter.

People with diabetes are at risk of COVID-19 infection may be due to the high proliferation of the virus due to unmetabolized glucose. A characteristic of some COVID-19 patients is coagulopathy (Tang et al. 2020a). Anticoagulant therapy with low molecular weight heparin had better prognosis in severe COVID-19 patients that were associated with high mortality (Tang et al. 2020b). Platelets, produced by the megakaryocytes of the bone marrow is responsible for blood clotting. Glucose is taken up through the platelets mediated through the glucose transporters GLUT1 and GLUT3. Lack of glucose transporters in the platelets reduce its counts and increase clearance of platelets (Fidler et al. 2017). Normal glucose reduces platelet activation; whereas, hyperglycemia increases platelet glucose metabolism thereby contributing to increased platelet activation and thrombosis in animal models of diabetes (Fidler et al. 2019).

Some of the COVID -19 patients have lungs that are not effectively oxygenating the blood (hypoxia), but feel alert and healthy and hardly gasp for breath. Glucose transport is acutely stimulated by hypoxic conditions, and the response is mediated by enhanced function of the facilitative glucose transporters GLUT (Zhang et al. 1999; Wood et al. 2007). Prolonged exposure to hypoxia results in enhanced transcription of the GLUT1 glucose transporter gene, with little or no effect on transcription of other GLUT genes (Zhang et al. 1999).

Several pulmonary disorders are associated with a decrease in alveolar oxygen tension and Alveolar epithelial cells (AEC) exhibits different adaptive mechanisms to cope with oxygen deprivation. Under hypoxia, because of inhibition of oxidative phosphorylation,

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adenosine triphosphate supply is dependent on the ability of cells to increase anaerobic glycolysis. Hypoxia induces stimulation of Na-independent glucose transport and increase in 2-deoxy-D-glucose (DG) uptake; it also induces the glucose transporter, GLUT1 at both protein and mRNA levels (Ouiddir et al. 1999). HIF-1α regulates the activity of glucose transporters, GLUT, that are responsible for glucose uptake. Hypoxia-inducible factors (HIFs) are oxygen-sensitive transcription factors that allow adaptation to hypoxic environments (Sadlecki et al. 2014). HIF-1α reduces acute lung injury by optimizing carbohydrate metabolism in the alveolar epithelium (Eckle et al. 2013).

An early characteristic of COVID-19 patients is loss of smell. The glucose receptors, GLUT is expressed in taste receptor cells (Merigo et al. 2011). Glucose receptors are expressed in the olfactory bulb and its changes may influence olfaction (Al Koborssy et al. 2014). Whereas, Villar et al. (2017) demonstrated that glucose removal and the inhibition of glycolysis or oxidative phosphorylation inhibits odor.

The data described in this paper are based on *in silico* analyses; homology models and similarities with plant and bacterial glucose transporters are not adequate to assign role of the M protein of the virus to specific host comorbidities such as diabetes. Further biological experiments are required to validate the presence and function of the virus membrane sugar transporter.

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Conflict of interest

The author declares no conflict of interest.

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Figures:

Fig.1. The protein sequence of the M glycoprotein of SARS-CoV-2. The sequence was downloaded from NCBI protein database.

QJA17755.1 membrane glycoprotein
[Severe acute respiratory syndrome coronavirus 2]

1 madsngtitv eelkklleqw nlvigflflt wicllqfaya nrnrflyiik liflwllwpv
61 tlacfvlaav yrinwitggi aiamaclvgl mwlsyfiasf rlfartrsmw sfnpetnill
121 nvplhgtilt rplleselvi gavilrghlr iaghhlgrcd ikdlpkeitv atsrtlsyyk
181 lgasqrvagd sgfaaysryr ignyklntdh ssssdniall vq

Fig. 2. Predicted M protein structure using the software SWISS-MODEL. The (A) ribbon representation, (B) spacefill and (C) surface models of the M protein of SARS-CoV-2.

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Fig. 3A. Membrane topology of proteins (snake diagrams) determined using Protter. (A) The membrane (M) glycoprotein of SARS-CoV-2 has a triple helix bundle, and formed a single 3-transmembrane domain. (B) Snake diagram of envelope (E) protein, (C) nucleocapsid (N) protein, and (D) spike protein (S).

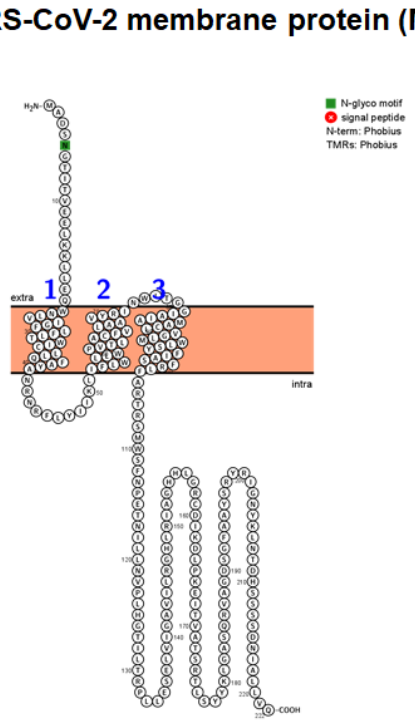

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Fig. 3B

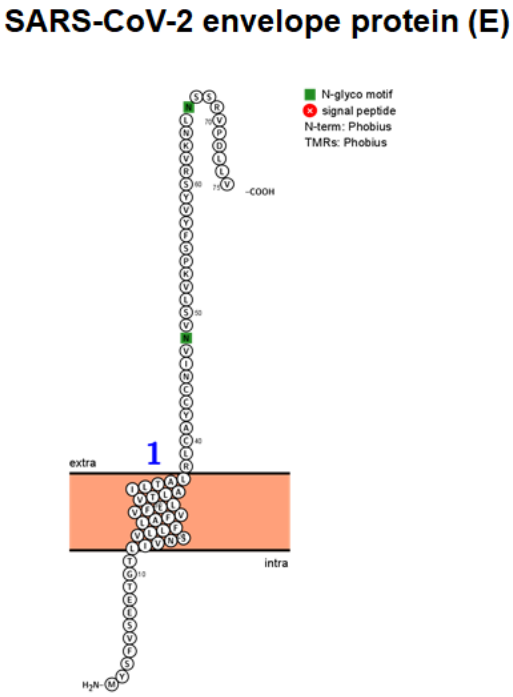

Fig. 3C

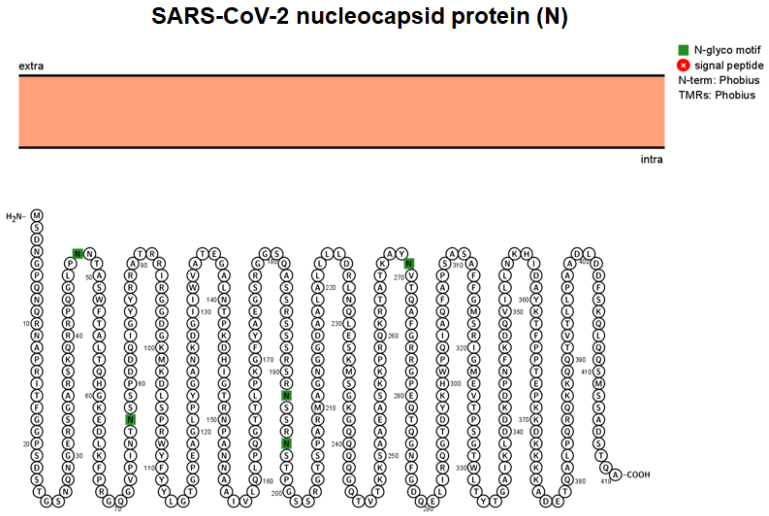

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Fig. 3D

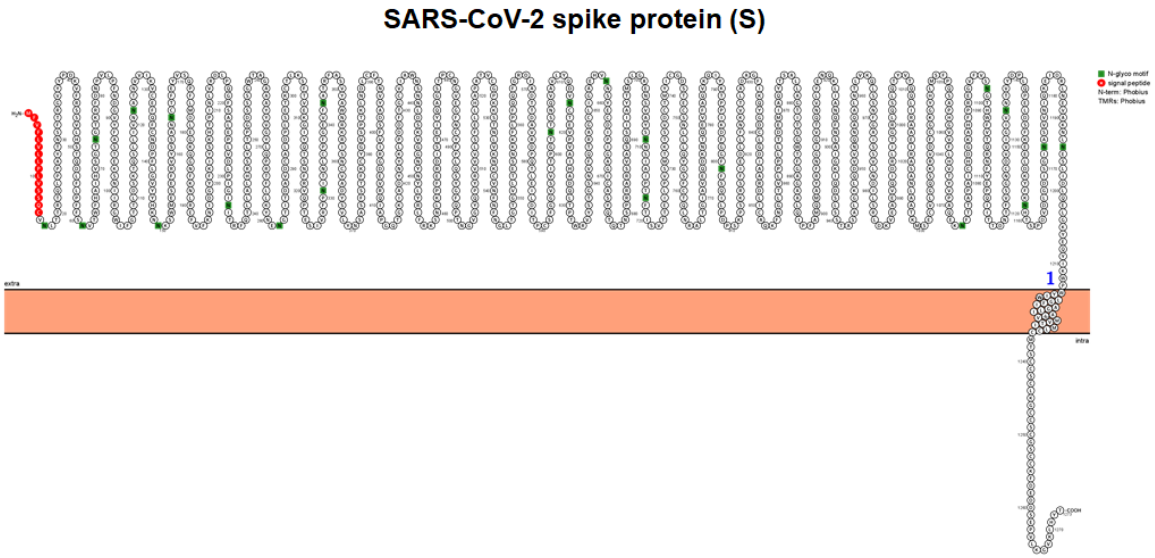

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Fig. 4. Protein sequences were aligned using ClustalW. Comparison of protein sequence of the M protein of SARS-COV-2 with (A) M protein of Bat SARS-CoV, (B) M protein of pangolin SARS-CoV, (C) M protein of SARS-CoV, and (D) MERS-CoV.

4A.

```
CLUSTAL O(1.2.4) multiple sequence alignment


QJA17755.1      MADSNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPV    60
QHR63303.1      -MADNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPV    59
                   .************************************************************

QJA17755.1      TLACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL    120
QHR63303.1      TLACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL    119
                ************************************************************

QJA17755.1      NVPLHGTILTRPLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSYYK    180
QHR63303.1      NVPLHGTILTRPLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSYYK    179
                ************************************************************

QJA17755.1      LGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALLVQ      222
QHR63303.1      LGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALLVQ      221
                ****************************************
```

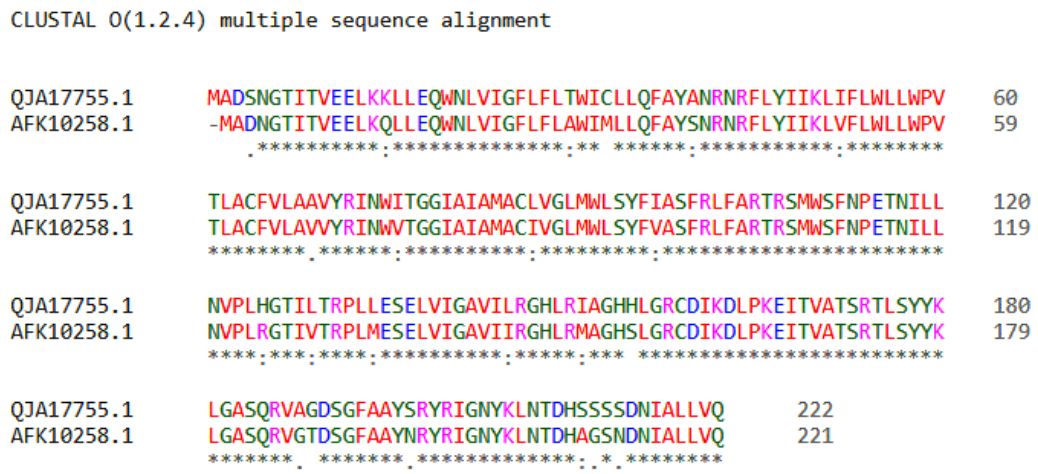
QJA17755.1: Membrane protein SARS-CoV-2
QHR63303.1: Membrane protein [Bat SARS CoV RaTG13]
Percent identity: 98.64

4B.

```
CLUSTAL O(1.2.4) multiple sequence alignment


QJA17755.1      MADSNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPV    60
QIG55948.1      MSGDNGTITVEELKKLLDQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPV    60
                *:..************:****************************************

QJA17755.1      TLACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL    120
QIG55948.1      TLACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL    120
                ************************************************************

QJA17755.1      NVPLHGTILTRPLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSYYK    180
QIG55948.1      NVPLHGTILTRPLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSYYK    180
                ************************************************************

QJA17755.1      LGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALLVQ      222
QIG55948.1      LGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALLVQ      222
                ****************************************
```

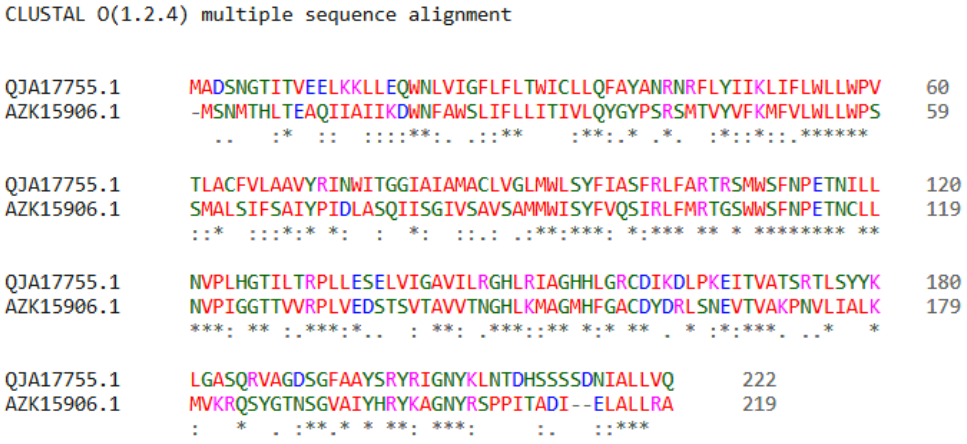
QJA17755.1: Membrane protein SARS-CoV-2
QIG55948.1 : Membrane glycoprotein [Pangolin coronavirus]
Percent identity: 98.2

4C.



QJA17755.1: Membrane protein SARS-CoV-2
AFK10258.1: Membrane protein [SARS coronavirus HKU-39849]
Percent identity: 89.14

4D.



QJA17755.1: Membrane protein SARS-CoV-2
AZK15906.1: Membrane protein [Middle East respiratory syndrome-related coronavirus]
Percent identity: 38.36

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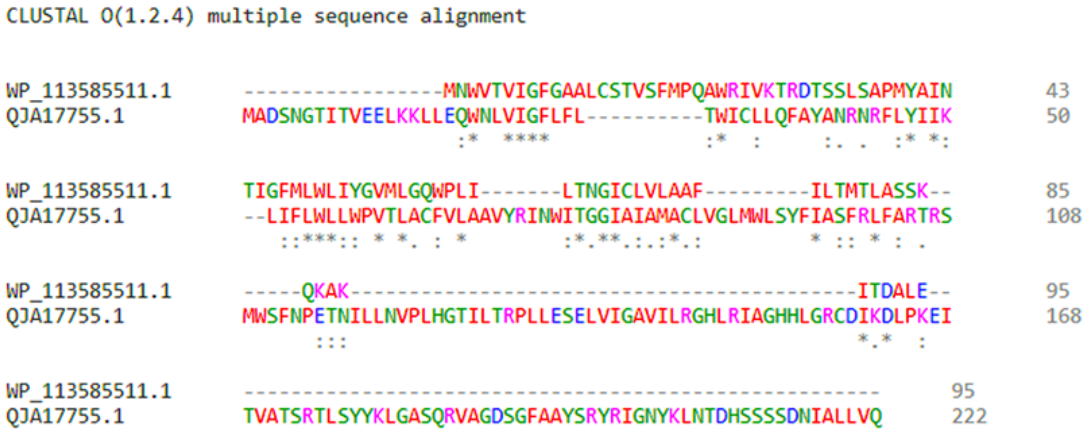
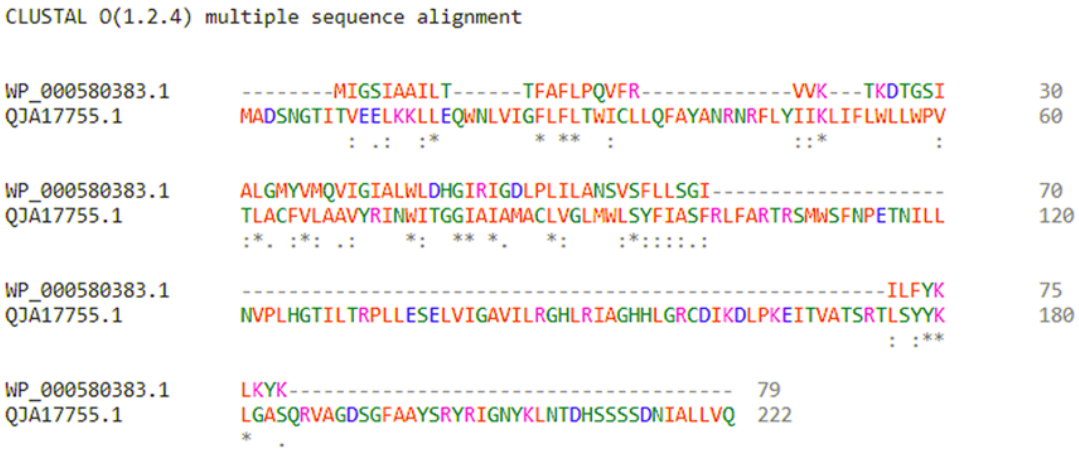
Fig. 5. Protein sequences were aligned using ClustalW. (A) Comparison of protein sequence of the M protein of SARS-COV-2 with semiSWEET sugar transporter of Rhizobiales. (B) Comparison of protein sequence of the M protein of SARS-COV-2 with semiSWEET sugar transporter of *Streptococcus pneumoniae.*



WP_113585511.1: semiSWEET Rhizhobiales
QJA17755.1: Membrane protein SARS-CoV-2
Percent identity: 26.51

Fig. 5B



WP_000580383.1: semiSWEET *Streptococcus pneumoniae*
QJA17755.1: Membrane protein SARS-CoV-2
Percent identity: 20.25

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Table 1. Homology of the M protein of SARS-CoV-2 with the M protein of other coronaviruses and the sugar transporter SWEET

Membrane Protein	Membrane protein identity (with SARS-CoV-2)	Bidirectional sugar transporter SWEET identity
SARS-CoV-2	100	14.3
Bat SARS-CoV	98.64	14.3
Pangolin SARS-CoV	98.2	14.3
SARS-CoV	89.14	14.3
MERS-CoV	38.36	20.0