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COVID-19 Genome and Pathogenesis; A Short Review

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Abstract: **The emerging COVID-19 has reached a pandemic level shortly fter the first few detected cases in Wuhan, China. The knowledge of the genetic assembly, mode of replication, transmission, and pathogenesis are cornerstones in the combat against this pandemic. In this short review authors highlighted the main up-to-date information on the abovementioned aspects of the virus, in addition to the major symptoms, and also a highlight of an adapted clinical management held in Sudan, Africa.**

Keywords: **COVID19, Genome, Viral RNA, Pathogenesis.**

1. INTRODUCTION; COVID RNA STRUCTURE

The covid-19 is a positive single stranded RNA virus (ribonucleic acid) [1], that contains phosphate and ribose sugar and the nitrogenous bases Adenine, Uracil, Guanine and Cytosine. It's a polynucleotide of 32 kilobases (32000), that synthesizes 11000 amino acids open reading frames (ORFS). This RNA is linked by phospho-diester and N-glycosidic bonds. Coronavirus RNA is different from human RNAs in that mRNA in human after, transcription (synthesis of RNA) is processed and modified and protected by added of 5' cap (methyl GTP) help movement of RNA from nucleus to cytosol and protect mRNA from endo-nucleases and ions binding like (Zn,Mg,Na) which can react with the phosphate groups. The tail of the RNA is covered by poly-A; Adenine bases of 20 up to 200 in number [2]**.** Coronavirus RNA doesn't contain 5 cap, or proceeding modification mechanisms [3], initiation factor two in transfer RNA (tRNA) prevent ions binding in position 5' because zinc can bind with the phosphates through iono-statistic bonds and prevent its function . Messenger RNA (mRNA) in man contains 61 codons and 3 acts as stop codon [4]**.**

Coronaviruses are coated by:

- Phospholipids such as phosphotidyl serine, choline, inositol, sphingomylein.
- Cholesterol, and
- Spike protein.

The lipid gives the virus a high molecular weight; for this reason virus can fall down into ground. The lipid bi-layer in corona viruses has an inherent tendency to be extensive, for this reason subjects need to clean their hands many times by using soaps. It may be good if they use sulfur soaps or alcohol, because phospholipids and cholesterol in membrane of virus are heterogeneous compounds; soluble in organic solvents like alcohol and virus can be damaged. Lipid bi-layers in corona will tend to close on themselves so that no edge are found with an exposed hydrocarbon chain so they form compartment, which make virus survive up to three days in hard surfaces.

Corona viruses are members of two subfamilies of Coronavirinae and Torovirinae in the family of Coronaviridae, which in turn comprise the order Nidovirales. The Coronavirinae subfamily is further classified into four main genera: a-coronavirus, b-coronavirus, g-coronavirus and d-corona virus based on the International Committee for Taxonomy of Viruses. HCoV-229E and HCoV-NL6 belong to a-corona virus, HCoV-HKU1, SARS-CoV, MERS-CoV, and HCoV-

OC43 are b-corona viruses, and they both infect only mammals. Gamma (g-Corona virus) and delta (d-coronavirus) infect birds [5]**,** but some of them can also infect mammals. Based on current sequence databases, it has been discovered that all human CoVs have animal origins; SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-229E are considered to be originated in bats [6**]**; HCoV-OC43 and HKU1N are likely originated from rodents [6]. Under the electron microscope, corona viruses are enveloped, single-stranded positive-sense RNA viruses with the largest genome size (ranging approximately from 26-32 kilobases) in viruses, found to date [7]. The genomic RNA, which acts as a messenger RNA (mRNA), plays an important role in the initial RNA synthesis of the infectious cycle, Template for replication and transcription and as a substrate for packaging into the progeny virus. In all CoVs, the 5' end two-thirds of the genome encodes a replicase polyproteins, pp1ab [8], which is comprised of two overlapping open reading frames (ORFs), ORF1a and ORF1b. These ORFs are then processed by viral proteases zinc dependant to cleave into 16 non-structural proteins that are involved in genome transcription and replication. The 3' terminus encodes CoV canonical set of four structural proteins. The genome organization is 5-leader-UTR-replicase-S (Spike)-E (Envelope)-M (Membrane)-N(Nucleocapsid)-3′UTRpoly (A) tail with accessory genes interspersed within the structural genes and the 3 end of the genome, a highly hydrophobic protein that covers the entire structure of the corona virus that prevent virus move in blood [9]. These accessory proteins are not only important for virion assembly but may also have an additional link that they suppress the host immune response to facilitate viral replication. The replication of corona virus begins with the binding of its spike protein (S) on the cell surface molecules of the host. This receptor recognition is important for initiating virus entry into the host cells, thereby playing a major role in the tissue and host species tropism of viruses. The receptors used by all human Coidv 19 is angiotensin-converting enzyme 2 (ACE2) [10], and also by SARS-CoV and HCoV-NL63 and dipeptidyl peptidase 4 (DPP4) by MERS-CoV. Apart from this, some CoVs may also enter into the cells with the help of proteases; for example, the role of cathepsin L has been linked with the SARS-and MERS-CoVs entry, transmembrane protease serine 2 (TMPRSS2) and airway trypsin-like protease TMPRSS11D that could activate the S protein for virus entry at the cell membrane during HCoV-229E and SARS-CoV infection [11]. Upon the entry, the viral particle is uncoded and then ready for translation ORF 1a and 1b into polyproteins pp1a (4382 amino acids) and pp1ab (7073 amino acids) that are processed by proteases 3-C-like protease (3CLpro) and papain-like protease (PLpro) all proteases require zinc. Subsequently, these polyproteins are cleaved into at least 16 nonstructural proteins (NSPs), which assembles and form the replication transcription complex. With the aid of replicases, the full-length positive strand of genomic RNA is transcribed to form a full-length negative-strand template for the synthesis of new genomic RNAs [12**].** These mRNAs are then transcribed and translated to produce the structural and accessory proteins'.

Coronaviruses goal is to enter to lung cells or intestine cells (ACE types two), bind with 80s ribosomal RNA of the host, and produce its own protein using the host tRNA [13].

2. THE MODE OF TRANSMISSION

2019-nCoV is thought to be transmitted through droplets, close contact, aerosol and maybe fecal-oral transmission, and patients in the incubation period can transmit the virus to other persons. The air droplets of the virus can stay for hours or days and then fall down by gravity because of the virus' high molecular weight. Virus by inhalation via nose then nasopharynx to the lungs. The prerequisite of corona viruses invading the host-cell is to bind to receptors. The viral spike protein is cleaved via acid-dependent proteolysis by cathepsin, TMPRRS2 or furin protease, followed by fusion of the viral envelop to the cellular membranes. Spike is a large, clove-shaped three dimensional, which can be cleaved by proteases into an N-terminal S1 subunit containing the receptor binding domain (RBD) and a C-terminal S2 region. Virus can enter to lung cells by endocytosis because of lung cells are very rich with phospholipids and virus also contain lipids, sphingolipid in virus has endothelial function and acts as ligand for receptor. After virus enter the cells phosphplipases A,C,D,E hydrolyze the virus membranes. Then positive RNA of virus carries the genetic code then occupied ribosome RNA of human 80s (40s +60s) and produces its' different types of proteins and open reading frames (ORFS); ORF-1a and ORF-1b [14].

3. REPLICATION OF THE VIRUS

The cell surface receptor has three mechanisms: ion –channel receptor; trans-membrane protein receptor (COVID-19 dependant); and kinase receptors. The virus first uses poly-A tail to enter and occupy the host ribosome RNA 80s; this criterion is specific in coronaviruses. The mRNA of the virus acts as template and produces many types of protein open reading frame ORFs , ORF1a and ORFIb [14]. The virus has specific protein (peripheral) receptor in lung cells like cell

membrane (trans membrane protein receptor) Angiotensin converted enzyme type two, which is actually a protease enzyme containing serine. It uses the spike protein in virus as substrate and hydrolyze it, then virus release RNA, phosphotidyl serine in virus acts as director to the receptor because receptor contain serine (protease enzyme contain serine, ORF 1a and 1b into polyproteins pp1a (4382 amino acids) and pp1ab (7073 amino acids) (genetic code 32000 kilobases that are processed by proteases 3-C-like protease (3CLpro) and papain-like protease (PLpro). The ORF6 prevents infected cell from sending any signal to immune systems, indeed, most of deaths in corona virus are due to cytokine storm. After virus had replicated and coated by lipid and protein, the cell try toprevent this virus to move out and produces Tethering protein which ORF7a bind to. With this protein thereafter more virus move out of the cell and also this protein has ability to damage the cell and causes chronicity to patients. Some ORFs are hydrolyzed by proteases to produce 16 types of proteins is called non structural protein (nsp); this name is because these proteins does not have the ordinary protein levels of structure. NSP1 (non structural protein 1) inhibits protein synthesis in human cells and prevent cell from antiviral proteins formation. NSP3 (non structural protein 3) is a big protein that change normal human proteins shapes. NSP 4 protects new virus which replicated form DNA. NSP5 has a cleavage protein property. NSP9 has ability to enter nucleus carrying the genetic materials of human to virus. NSPs 12, 13,14,15,16 has role in inhibiting immunity. nsp10 represents a novel fold and is the first structural representative of this family of Zn finger proteins found so far exclusively in coronaviruses.

Corona virus RNA interference provides an Additional tool for disrupting gene expression. When a double stranded RNA molecule (large size) is introduced into an appropriate cells the RNA is cleave by an enzyme referred to as Dicer into fragments nucleotides each consist of double stranded RNA (small fragments) and some bases of paired like UUUU with AAA template with negative sense. After separation, the two single-strand RNA, termed small interfering RNA (SIRNA) are each incorporated into different enzyme refer to as RNA –induced silencing complex (RISC) The single RNA. This mechanism happens after positive RNA synthesized protein and then binds with negative RNA to produce more positive RNA. All non structural protein is converted into structural protein in Golgi apparatus. the protein(nsp) enter to Golgi apparatus to modify, into(sp) structural protein this apparatus composes of intracellular space or cytosol and extracellular space ,the function of the apparatus can add to virus cholesterol, glycolipid protein and GPI can anchored protein to make it in primary ,secondary ,tertiary and quaternary (spike) protein and membrane and envelope protein . The second skeletal protein is composes of lipids like cholesterol and phospholipids and could be damaged by organic solvents like alcohol even soaps. Phosphotidyl lipase D trafficking through Golgi, and transfer the phosphotidyl moiety to variety of alcohol and transphosphotidylation to synthesis of phospholipids, Phospholipas D has role in endocytois and lysosome membrane fusion, phosphotidyl inositol 3 kinase is regulated lipid metabolism and cytoskeltal structure of virus then know virus contain phospholipids, protein and cholesterol and RNA, know virus can move out by exocytosis

4. COVID 19 GENOME

On the basis of the genome sequences obtained, a real-time PCR detection assay was developed. PCR primers and probes were designed using Applied Biosystems Primer Express Software (ThermoFisher Scientific, Foster City, CA, USA) on the basis of our sequenced virus genomes. The specific primers and probe set (labelled with the reporter 6-carboxyfluorescein [FAM] and the quencher Black Hole

Quencher 1 [BHQ1]) for *orf1a* were as follows: forward primer 5′-AGAAGATTGGTTAGATGATGATAGT-3′; reverse Primer 5′-TTCCATCTCTAATTGAGGTTGAACC-3′; and probe 5′-FAM-TCCTCACTGCCGTCTTGTTGACCA-BHQ1-3′.The human *GAPDH* gene was used as an internal control (forward primer 5′-TCAAGAAGGTGGTGAAGCAGG-3′;reverse primer 5′-CAGCGTCAAAGGTGGAGGAGT-3′;probe 5′-VIC-CCTCAAGGGCATCCTGGGCTACACTBHQ1-3′). Primers and probes were synthesized by BGI(Beijing, China). RT-PCR was done with an Applied Biosystems 7300 Real-Time PCR System (Thermo-Scientific),with 30 µL reaction volumes consisting of 14 µLof diluted RNA, 15 µL of 2X Taqman One-Step RT-PCR Master Mix Reagents (4309169; Applied Biosystems)

ThermoFisher), 0・5 µL of 40X Multi-Scribe and RNAse inhibitor mixture, 0・75 µL forward primer (10 µmol/L),0・75 µL reverse primer (10 µmol/L), and 0・375 µL probe (10 µmol/L). Thermal cycling parameters were 30 min at 42°C, followed by 10 min at 95°C, and a subsequent40 cycles of amplification (95°C for 15 s and 58°C for 45 s).Fluorescence was recorded during the 58°C phase.

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5. PATHOGENESIS

Corona virus is zoonotic, i.e. a virus transmitted from animals to humans and recently from human to human through respiratory droplets or cough or contaminated hands the virus enter to GIT or lung via inhalation the virus may be stay for three days in nasopharyngeal if it dry, after that enter to lung cells by tarnsmembrane receptor is called ACE type two in lung cells [15]. There are two lung cells type one alveolar cells which is responsible for Gas exchange and type two is macrophage cells and produce lung surfactant like protein and lipid and sugar it acts as defense line. The virus has spike protein acts as substrate to enzyme ACE type two is protease enzyme very rich with serine ,the virus contain phospholipids ,phosphotidyl serine recognized the virus to ACE the receptor is called protease enzyme serine, then virus replicated some protein like ORF help virus move out ,the virus damage alveolar cells type two ,the macrophage try to produce cytokines like interleukin 1 and 6 and 10 and Tumor necrosis factor for this reason patient come with high interleukins but this inflammatory mediators damage the cells. Vasodilatation occur near type one alveoli which responsible for gas exchange, and this lead to increase capillary permeability and fluid between blood vessels and alveolar decrease gas exchange and this lead to short of breathiness or hypoxia or hypoxemia, the virus after damage type two alveolar surfactant is decrease and this lead to lung collapse , some fluid enter to alveoli and cause edema and patient come with cough or productive cough [16]. After lung collapse and edema patient developed acute respiratory syndrome (ARS) there after cytokine release later because virus produced ORF and nsp to suppress immune system this cytokine like neutrophil are produce Reactive ox gene species' but this also damages the cells for this reason patient come with high neutrophils. After destroyed alveoli the fluid will increase and lead to consolidation productive cough and hypoxia and ORD some virus enter to lymph system and caused lymphopenia and some virus enter to blood the immune system reacted with virus and this reaction caused pulmonary embolism .CNS When type two cell damage the interleukin 1 and 6 and 10 will librated and these inflammatory mediators make hypothalamus produce prostaglandin this hormone converted energy into heat by increase the metabolic rate and causes high grade fever and also lead to severe brain stroke especial among adults due the reaction of virus against immune storm .Hypoxia that means low oxygen which stimulate peripheral chemo receptor and this accelerate sympathetic and increase heart rate tachycardia ,the blood pressure is decrease which lead to decrease blood volume then perfusion will decrease and this lead to multisystem failure .

Also hypoxia affect blood volume and plasma and organ perfusion will decrease and lead to organ injuries like liver and kidney which increases their functionsand this affected D-dimer will be Increased Albumin will be Decreased and Alanine aminotransferase Aspartate aminotransferase will be Increased

Total bilirubin, blood urea nitrogen, and serum creatinine will be Increased and Creatine kinase will be decreased .the shortage of oxygen make organ on aerobics mechanism usually the organs produced high level of lactate .

- **Corona virus in GIT**

Corona virus enters via GIT in stomach. HCl can't denature some spike protein 75% and some viruses move to intestine in brush of intestine there trans-membrane receptor is called A CEtype two is protease enzyme is similar to ACE in lung both acts on glycoprotein and similar to carboxyl peptidase (acts on)protein zinc contain this virus damage epithelial and endothelial of mucosa and caused diarrhea 25% some virus enter to lymphatic in intestine and caused lymphopenia because of this virus similar to micelle like chylomicron also move via lymphatic system to blood and this contain hydrophilic protein but corona contain hydrophobic for this reason cant appear in plasma more than two days and also half life to ACE type two in blood two hours ,if virus replicated can move in stool and caused diarrhea.

- **Corona virus in blood**

Corona virus can bind with ACE type two in intestine or lung That mean corona virus resist Hcl in stomach and move to intestine and replicated and some group move with stool and some group invade lymphatic system and caused lymphopenia and ACE type two is transmembrane enzyme can stay two hours in blood with virus then virus stay in blood and attack by cytokines storm and this can cause clotting disorder in blood vessels Activated partial thromboplastin time and Prothrombin time will be decreased an Leucocytes d elevate and Platelets decreased due to haemolysis RBCs will be ruptured and increased Serum ferritin same mechanism can occur in brain and can cause cerebral stroke ,in lung can cause pulmonary embolism and MI and the main cause of death the reaction between virus and cytokines storm in blood vessels .

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- **Corona virus in eye**

Can lead to conjunctivitis

- **Corona virus in skin,**

Can lead to redness of skin and pain toes (Covid toes).

6. CLINICAL SYMPTOMS OF 2019-NCOV INFECTION

The clinical symptoms of 2019-nCoV infection are similar to those ofSARS-CoV and MERS-CoV. Most patients present fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans. However, patients with 2019-nCoV infection rarely have obvious upper respiratory signs and symptoms (such as snot, sneezing, or sore throat), indicating that the virus primarily infects the lower respiratory tract. In addition, about 20 – 25% of 2019-nCoV patients experience intestinal symptoms and signs (such as diarrhea), similarly to MERS-CoV or SARS-CoV. In severe 2019-nCoV infection cases, the symptoms include acute respiratory distress syndrome, septic shock, metabolic acidosis, and bleeding and coagulation dysfunction. It is worth noting that severe and critically ill patients may have moderate to low fever during the course of the disease, even without obvious fever]. Furthermore, like SARS-CoV and MERS-CoV, 2019-nCoV infections induce production of high levels of cytokines .The epidemic of 2019-nCoV bears some similarities to SARS-CoV. The outbreaks of the two viruses occurred at about the same time during the year, and they were quite stable in the environment, especially in air-conditioned spaces, owing to lower ambient temperatures and lower humidity. However, SARS-CoV had an aberrant atrait in that the “viral load” in upper respiratory tract secretions was low in the first 5 days of illness, then increased progressively and peaked early in the second week. Consequently, the transmission rate was relatively low in the first days of illness, providing an opportunity for case detection and isolation to interrupt transmission. On the contrary, for 2019-nCoV, the incubation lasts an average of 10days (in a reported range of 2-14 days) from infection to symptoms surfacing. Even worse, 2019-nCoV is able to spread from one person to another even before any actual clinical manifestations, leading to “extremely challenging “conditions for detecting and isolating potential patients, which makes it more difficult to control the epidemic.

7. UMMDAGARSI PROTOCOL AGAINST COVID- 19

This management protocol achieved good results in Sudan.

1-hydroxy chloroquine 200mg p.o BID (Two times daily) for seven days

This drugs is a protonate that change the pH of Golgi apparatus and prevent posttranslational of protein synthesis in virus nsp cannot converted into structural protein checkup ECG

2-aspirin 100 mg p.o (per oral) once

To prevent stroke that reaction occur between virus and cytokine storm,In severe cases inj, Enoxaparin 1mg per kg subcutaneously Bid or heparin iv 5000 iu for 5days and follow INR

3-Azithromycin 500 mg p.o once daily for days to exclude secondary infection like pneumonia and septic shock

Avoid amoxicillin prevent hydroxy chloroquine absorption

4-multiple vitamins particularly vitamin D and C

5-Zinc sulphate 50mg BID p.o for 15 days

To stop diarrhea, and accelerate immune system, to inhibit replication of virus zinc bind with nsp 10

And bind with of virus and inhibit function .the corona virus usually consume zinc ,znic help vitamin D absorption zinc finger, increasing the intracellular Zn2+ concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza viruses,More specifically, Zn2+ was found to block the initiation step of EAV RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced.

Zinc is a dietary trace mineral and is important for the maintenance and development of immune cells of both the innate and adaptive immune system [17]. Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity

and increases susceptibility to infectious diseases [18], Zinc supplement given to zinc-deficient children could reduce measles-related morbidity and mortality caused by lower respiratory tract infections [19]. Increasing the concentration of intracellular zinc with zinc-ionophores like pyrithione can efficiently impair the replication of a variety of RNA viruses.44 In addition, the combination of zinc and pyrithione at low concentrations inhibits the replication of SARS coronavirus (SARS-CoV) [20]. Therefore, zinc supplement may have effect not only on COVID-19-related symptom like diarrhea and lower respiratory tract infection, but also on COVID-19 itself, Zinc –bindig of the cysteine-rich domain encoded in open reading frame of the RNA polymerase gene of CORONA virus.

8. THE USES OF NATURAL PRODUCTS AGAINST COVID-19

The following ingredients were recommended by Gasmalbari et al. (2020) in the management of COVID-19 21: A*cacia nilotica*, Zingiber officinale, Cinnomomum, Cipmpinella, Nigella Sativa, Honey, and Sudan peanuts. These natural nutrients are very rich with:

- ***Alkaloids:*** Corona virus covid -19 when occupied cell is produced non structural protein (nsp) may be polyamine react with nsp and prevent virus function viruses other drugs like peptide 55,56,57,and 58 this polyamine are used against covid -19
- ***Polyphenols:*** Inhibit fats cell formation, and protein of virus
- ***Glycosides:*** Corona virus contain N-glycolicsidic bond between sugar and base may be Glycosides biding and inhibit replication .
- ***Terpenes:*** These act like steroid usually corona virus affected lung cells and caused edema, edematous lung is treated by steroid ,terpenes
- ***Saponins:*** Overdose of saponin can lead to heamolysis especially in Acacia Nilotica after 21 days
- ***Tannins:*** Covid -19 move to intestine in brush of intestine there is transmembrane receptor is called A CE type two is protease enzyme is similar to ACE in lung both acts on glycoprotein and similar to carboxyl peptidase acts on protein zinc contain this virus damage epithelial and endothelial of mucosa and caused diarrhea 25% may be this tannins denature protein of virus spike shape
- ***Coumarin:*** Corona virus in the lung could cause pulmonary embolism ,the best treatment for this complication is heparin and warfarin which both are derived from coumarin ,also this this coumarin acts as anti-coagulant and hemorrhagic
- ***Flavonoids:*** Act as thermogenic compounds, anti-oxidant activity, have antiviral abilities, some flavonoids inhibition of 3C-like protease this enzyme in covid -19
- ***Sudan peanut:*** is very rich with arachidonic acid which accelerate immune system biosynthesis

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