ABSTRACT

The Severe Acute Respiratory Syndrome Coronavirus-2, originated in Wuhan, China in late 2019 has created a massive pandemic; the disease manifested by the virus was named as COVID-19 by World Health Organization. It has appeared as an unprecedented threat against the global health scenario, as well as the world socio-economic-political structure. The infection of the plausibly animate-origin virus, per se, is not dangerous; but its extremely contagious and infectious nature is the major challenge it has posed. In human, the viral receptor is angiotensin converting enzyme-2, which is present in the cellular membranes of multiple vital organs. The virus has different longevity in different contaminated surfaces which are the principal modes of its transmission. No immunity has so far been reported against the virus; however, immuno-compromised individuals are more vulnerable. For its diagnosis, mainly reverse transcription-based diagnosis is presently being used; however, serological diagnosis is still not a regular practice due to several reasons. Multiple public...
as well as private sector organizations are working towards vaccine development; research for antiviral drugs and drug-repurposing is also in progress. Several candidate vaccines and drugs are now in various levels of clinical trials. Here, we summarize the scientific basis of the pandemic; its diagnosis, treatment and efforts towards therapeutic development. These efforts will prove useful against future emerging and re-emerging human and non-human epidemics as well as pandemics.

Keywords: SARS-CoV-2; COVID-19; therapy; treatment; coronavirus.

1. INTRODUCTION

The ongoing pandemic of COVID-19, reportedly caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is possibly one of the major pandemics in the history of human civilization. The disease broke out in the city called Wuhan in Hubei province of China in December 2019; till mid July, 2020, infection has been reported in 213 countries infecting more than 14 million people, causing nearly 593 thousand deaths worldwide. The coronavirus associated with the pandemic was identified as a member of the Genus, betacoronavirus; the earlier known Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome (MERS) virus are also members of the same genus [1]. The World Health Organization declared the disease-situation as a Public Health Emergency of International Concern on 30th January; and later, as a pandemic on 11th March, 2020. Although, initially the disease caused by SARS-CoV-2 was referred by different names, subsequently, it was named as COVID-19 following existing guidelines. However, the pandemic is not a new outbreak; there had been three other flu-like pandemics in the last century. They were the 1918 flu pandemic (popularly known as Spanish flu), the 1957-1958 flu pandemic (popularly known as Asian flu) and the 1968 flu pandemic (popularly known as Hong Kong flu). The 1918 flu pandemic which was caused by the H1N1 Influenza-A virus have so far been the deadliest pandemics; lasting for more than 12 months, the virus infected around 500 million people and caused around 100 million deaths worldwide (however, these figures are disputed). The 1957-1958 flu pandemic and the 1968 flu pandemic killed nearly 2 million and 4 million people, respectively [2].

The COVID-19 outbreak has posed as a global threat to civilization. The economic, political, financial, social and religious structures of the planet have been disturbed due to the pandemic. The world’s top-order economies like the US, China, Japan, UK, Germany, France, Italy etc. are at the edge of collapse due to the outbreak, which is presumed to be the worst such disaster since World War-II. The advanced economies may experience an economic contraction in 2020 amounting up to about 7.8% of GDP; International Monetary Fund (IMF) predicts that the US economy itself may decline by 5.9%, which is about twice the decline rate faced during the financial crisis in 2009 [3]. The economic impact of this pandemic in India has been largely disruptive. India’s economic growth for the next fiscal year (i.e., 2021) has been downgraded by the World Bank and credit rating agencies as 1.5 to 2.8%, which will be the lowest that the country has experienced since economic liberalization in the 1990s [4].

Coronaviruses are members of the family, Coronaviridae, of the order, Nidovirales, and are known since 1960 [5]. They are named after the crown-like spikes on their surface. Coronaviruses infect vertebrates including humans, bats, birds, mice, snakes, mice and other wild animals [6-7]. There are seven known human coronaviruses (HCoVs) reported to be associated with respiratory diseases (HCoV–229E, OC43, NL63, HKU1, SARS-CoV, MERS-CoV and SARS-CoV2). The last three strains of HCoVs are the ones causing higher mortality rates in human populations than the other four [8]. The SARS-CoV was first identified in November 2002 in the Guangdong province of Southern China [6]. As in case of the latest SARS-CoV-2 outbreak, the SARS-CoV was also believed to get transmitted from animal hosts to human from the open markets in China [1]. Its outbreak was however contained in July 2003 [6]. The second coronavirus outbreak emerged as MERS in 2012 in Saudi Arabia and it immediately resulted in a major global public health crisis [2]. In the year 2013, a similar virus to SARS-CoV was discovered in horseshoe bats; it was named as bat SARS-CoV [9]. This discovery suggested that there might be another SARS outbreak if conditions are suitable for this dangerous virus to carry out its life cycle [10]. As the findings suggest, the wet markets in Wuhan, China trading large numbers and varieties of wild
mammals might have led to the transmission of the present novel coronavirus from animals to human [11]. This virus possesses the ability to propagate at an alarming rate, thereby resulting in disease clusters from a single index patient [12]. The capacity of the virus for human-to-human transmission, lack of awareness of management of the virus in the hospital, and international air travel opened the way for the global spread of this pathogen [10]. Till date, no effective vaccine or therapeutic has been discovered for effective prevention of the viral transmission or treatment the disease caused by it. The only way through which the SARS-CoV-2 outbreak got curbed was by maintaining strict quarantine and isolation [13]. This review is aimed to understand the genetics of coronavirus, various diagnostic techniques adopted for detection of the virus and the vast range of therapy that has potential to be applied for the treatment and management of the disease.

2. THE VIRUS

CoVs belong to the family, Coronaviridae (order Nidovirales). This family consists of a large number of positive-stranded RNA viruses. Under electron microscopes, CoVs exhibit a crown-like structure (coronam is the Latin means ‘crown’); the spike glycoproteins found on the envelope of the virus are majorly responsible for this distinctive structure of the viruses. The family includes a subfamily called Orthocoronavirinae along with several yet-to-be-classified coronaviruses. The subfamily, Orthocoronavirinae is again grouped into four genera: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV), and several unclassified coronaviruses [14]. While bats and rodents have been reported to be the carriers of alphaCoVs and betaCoVs, deltaCoVs and gammaCoVs are probably carried by birds. SARS-CoV-2 is a member of the genus, Betacoronavirus, and has a round or elliptic and regularly pleomorphic structure with a diameter of approximately 60–140 nm.

Although the origins of SARS-CoV-2 are not completely clear, genomic analyses conducted by Chan et al. [15] suggests that SARS-CoV-2 presumably evolved from a strain reported in bats, primarily because it shares 89% nucleotide identity with a bat coronavirus (SARS-like-CoVZXC21) and 82% nucleotide identity with the earlier known SARS-CoV. The intermediate host between bats and humans is unknown [16] and it could be possible that there is no existence of any amplifying intermediary since the suspected mutation in the original viral strain could have legitimately triggered virulence towards people. However, epidemiological data suggests civets might have acted as intermediate hosts for SARS-CoVs and dromedary camels for MERS-CoV [17].

2.1 Transmission

The first report of human coronaviruses came in 1966 [18]. The virus caused infection in the upper respiratory tract of individuals including children in UK, and the virus was named as “B814”. In the following years, seven other coronaviruses infecting human have been identified; however, all of them have been found to not equally pathogenic. For example, while alphaCoVs such as HCoV (Human coronavirus)-229E and HCoV-NL63, and betaCoVs such as HCoV-HKU1 and HCoV-OC43 were reported to exhibit low pathogenicity (they also show mild symptoms) [19], the other three, i.e., SARS-CoV, MERS-CoV and SARS-CoV-2 (all belonging to the genus, Betacoronavirus) had shown high pathogenicity and transmissibility, and mild respiratory symptoms. The mortality rates of SARS-CoV and MERS-CoV were reported to be approx. 10% and approx. 35%, respectively [15].

For SARS-CoV-2, zoonotic transmission was assumed as the primary mechanism. However, since the cases subsequently reported were not related with this exposure mechanism, it was concluded that the human-to-human transmission of virus could happen via respiratory droplets and both asymptomatic carriers and the symptomatic people are the regular carrier of COVID-19 [20].

The primary mode of transmission of SARS-CoV-2 is from symptomatic individual carriers. Such transmission happens by means of direct contact with the infected individuals, close contact through respiratory droplets or then again by contact with contaminated surfaces [21]. Recent studies have indicated that viral shedding is the maximum in the upper respiratory tract from the initial three days from beginning of the symptoms [22]. Other modes of transmission include pre-symptomatic and asymptomatic transmission. Pre-symptomatic transmission alludes to transmission occurring not long before symptoms appear after infection; such transmission happens generally 1 to 3 days before the infected individual become symptomatic [23].
Asymptomatic transmission alludes to transmission during the incubation time frame that averages between 5 to 6 days; sometimes, up to 14 days [24]. Nevertheless, there has not been any report of asymptomatic transmission of SARS-CoV-2.

Studies conducted by several centres of disease control in Wuhan reports that the incubation time for SARS-CoV-2 is by and large within 3 to 7 days, sometimes, as long as about 2 weeks. The longest time taken from disease to symptom appearance has been found to be 12.5 days [21]. Their data showed the basic reproduction number ($R_0$) of COVID-19 as 2.2, which means on an average, a diseased individual spreads the infection to an additional 2.2 individuals [21]. However, in view of the analysis of high-resolution real-time human travel and infection data, Sanche et al. [25] reported that the $R_0$ is a lot bigger, extending from 4.7 to 6.6 before the control measures were adopted. Generally, an epidemic spreads when the $R_0$ is greater than 1; therefore, the control measures aim to reduce this value to less than [21].

2.2 Structure and Organisation of SARS-CoV-2 Genome

The ssRNA genome of SARS-CoV-2 consists of approx. 30,000 nucleotides and is modified with a 5' cap structure and a 3'-poly-A tail; it has the largest known RNA genome. The sequence of ORFs located in the RNA (from 5' to 3') is: ORF-1a/ab encoding nonstructural proteins (Nsps) for replication, spike (S), envelope (E), membrane (M) and nucleocapsid (N); several accessory proteins such as ORF-3b, 6, 7a/b, and 8b, 9a/b, 10 [26]. Its 5’ untranslated region (UTR) is 265 nt long and the 3'-UTR is 229 nt long. The ORF-1a/ab is approx. 21,300 nt in length and encode replicase polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively. Both of these polyproteins are proteolytically cleaved into 16 putative nsps encoding for non-structural proteins (Nsp-1 to Nsp-16), which structure the complex replication machinery. The genes that encode the components of the mature virus, i.e., S, ORF-3a, E, M and N are approx. 3,820, 830, 230, 670 and 1,260 nt in length; they play crucial roles in viral structure integrity or as in the case of the spike-protein, for viral entry in to the host [7] (Fig. 1).

Fig. 1. Genome organisation of SARS-CoV-2. The genome consists of open reading frames (ORFs) 1a and 1b, non-structural proteins genes (Nsps), structural proteins gene (S), envelope protein gene (E), membrane protein gene (M), nucleocapsid genes (N) and the accessory protein genes (3a,3b,7a,7b, 8b, 9a, 9b and 10) from 5’ to 3’. The figure was adapted from Romano M, Ruggiero A, Squeglia F, Maga G, Berisio R. A structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. Cells. 2020;9(5):1267 [28]
Table 1. Functions of non-structural proteins (Nsps) of SARS-CoV-2 involved in replication

| Proteins | Function |
|----------|----------|
| Nsp-1    | Inhibits translation in host cell resulting in blockage of innate immune response; degrades host mRNA. |
| Nsp-2    | No known function. |
| Nsp-3    | Interacts with N-protein, papain like protease PL1\(^{pro}\), PL2\(^{pro}\). Has ADP-ribose-1’-phosphate activity, promotes cytokine expression. PL\(^{pro}\)/Deubiquitinase domain is involved in cleaving of the viral polyprotein & blocking host innate immune response. Ubi2, NAB, G2M, SUD, Y domains: unknown function. |
| Nsp-4    | Potential transmembrane scaffold protein, important for proper structure of double-membrane vesicles. |
| Nsp-5    | Also called M\(^{pro}\)/3C-like protease, cleaves viral polyprotein. |
| Nsp-6    | Potential transmembrane scaffold protein. |
| Nsp-7    | Binds to single stranded-RNA; forms hexadecameric complex with Nsp-8; may act as processivity clamp for RNA polymerase. A primase and cofactor of Nsp-12. |
| Nsp-8    | Forms hexadecameric complex with Nsp-7; may act as processivity clamp for RNA polymerase; cofactor of Nsp-12. |
| Nsp-9    | RNA binding protein. |
| Nsp-10   | Cofactor for Nsp-16 and Nsp-14, forms heterodimer with both and stimulates ExoN (viral exoribonuclease) and 2-O-methyltransferase activity. |
| Nsp-11   | No known function. |
| Nsp-12   | RNA-dependent RNA polymerase. |
| Nsp-13   | RNA helicase, 5’ triphosphatase. |
| Nsp-14   | N-7 methyltransferase (adds 5’ cap to viral RNAs) and 3’-5’ exoribonuclease, ExoN (important for proofreading of viral genome). Also Guanine N-7 methyltransferase |
| Nsp-15   | Uridylyate-specific viral endoribonuclease, NendoU. |
| Nsp-16   | Shields viral RNA from Melanoma differentiation associated protein-5 recognition and 2’-O-ribose methyltransferase. |

(Adapted from https://www.discngine.com/blog/2020/3/27/sars-cov-2-2-from-the-viral-genome-towards-protein-structures)

The four structural proteins, i.e., S, E, M and N, play primary roles in the structure of the virus particle; they are also additionally engaged in other aspects of the replication cycle. The S-protein (approx. 200 kDa) adheres to the host cell surface receptors bringing about fusion and viral entry inside the Host. It also determines host and tissue tropism [31]. It makes a homotrimer making the distinct spike-like structure, and serves as a major target of neutralizing antibodies [32]. At the N-terminal region of S-protein, a globular S1-domain is present, which is trailed by membrane-proximal S2-domain, a transmembrane domain and an intracellular domain [33]. The S-protein is heavily N-linked glycosylated (that makes it a glycoprotein) and it obtains access into the endoplasmic reticulum through an N-terminal signal sequence. The S1-domain is the receptor-binding domain (RBD) of the S-protein and the S2-domain forms the stalk of the spike [34]. Also, the S-protein mediates cell-cell fusion among infected and adjacent uninfected cells forming multinucleated giant cells, resulting in direct viral spread between adjacent; in the same time, avoiding virus neutralising antibodies [35].

The most abundant structural protein of SARS-CoV-2 is the M-protein (approx. 25–30 kDa). This protein has three transmembrane domains [36]; it plays a central role in virus assembly and is principally responsible for providing the shape of the viral envelope. The M-protein has a special ability of assuming two alternate conformations; the two conformations are termed as M-elongated and M-compact. This versatility of M-protein allows the virus particles in promoting membrane curvature and thus binding to the nucleocapsid [37]. The M-elongated conformation provides higher rigidity and denser grouping of the spikes resulting in a narrower range of curvature of the membrane. On the other hand, the M-compact conformation is responsible for flexibility and lower spike density that provides a wider membrane curvature. The S- and N-proteins interact with the M-protein and regulate the size of the virions. It had been shown that the interaction between the S- and
the M-protein is essential for recognition of S-protein in the ER-Golgi intermediate compartment (ERGIC) / Golgi complex and its incorporation into new virions [38]. Similarly, the complex of the M- and the N-protein forms the viral core [39]. The M- and the E-proteins form the viral membrane and the interaction between these two leads to the formation and release of virus-like particles [40].

The transmembrane protein, E (approx. 8–12 kDa), is the smallest amongst the structural proteins. It plays an important role in viral assembly/budding. An N-terminal ectodomain and a C-terminal endodomain with ion channel activity have been reported to be present in this protein [36]. Nevertheless, it has been reported that during the replication cycle, E-protein expression occurs inside the ERGIC/Golgi membranes of infected cell; however, only a small portion of it is incorporated into the virus envelope [41]. It has been hypothesized that due to its role in virus morphogenesis and maturation, recombinant CoV lacking E-protein might serve as a decent contender for the development of a live attenuated SARS-CoV vaccine [42].

The only protein of CoV that binds to its RNA genome is the N-protein (nucleocapsid; approx. 46 kDa). The essential role of N-protein is genome encapsidation, i.e., to bundle the viral genome into a long, flexible and helical ribonucleoprotein complex called nucleocapsids. It is needed for timely replication and transmission of the virus [43]. It has three putative regions: an N-terminal domain, a RNA-binding domain and a C-terminal domain. The M-protein is additionally associated with the development of the nucleocapsid via interaction with the N-protein. The N-protein interacts with the carboxy-terminus of the M protein. Like the E-protein, the N-protein is associated in viral assembly and budding bringing about complete virion formation [44]. Other than its participation in virus life cycle, the N-protein also plays crucial roles in cellular responses like chaperone activity, cell cycle regulation, host translational shut-off by interaction with mammalian elongation factor-1α, viral pathogenesis by inhibiting the production of interferon and signal transduction [43]. Due to its high abundance in the host during infection, it is considered as a major antigen. This high antigenicity has earlier been utilised in the advancement of rapid-diagnosis kits against SARS-CoV [44].

2.4 Genetic Diversity and Evolution

The surprisingly fast spread of SARS-CoV-2 raised a very interesting question about the evolution of the virus and whether mutations or recombination was responsible for the same. It’s important to note that the SARS-CoV-2 is very similar to SARS-CoV in the amino acid level. The two viruses also share a highly conserved domain \((122\text{LLRKNNGK}_{130})\) in Nsp-1. The predicted ORF-8, located between the M and the N ORFs, also shares considerable similarity [16]. However, there also exist noteworthy differences between the two viruses. For example, the 8a protein found in SARS-CoV is missing in SARS-CoV-2. Likewise, while the 8b protein consists of 84 amino acids in SARS-CoV, it’s much longer in SARS-CoV-2 comprising of 121 amino acids. The 3b protein is composed of 154 amino acids in SARS-CoV, but it is much shorter in SARS-CoV-2 with only 22 amino acids [7]. Besides, compared to SARS-CoV, SARS-CoV-2 had 93 point mutations along the entire length of the genome. Among these 93 mutations, 42 missense mutations were detected in the major non-structural and structural proteins. Most of the mutations (29 mutations) were found in the ORF-1ab polyprotein; the other mutations detected were in S-protein (8 mutations), M-protein (1 mutation) and N-protein (4 mutations). Interestingly, 3 mutations (D\(_{354}\), Y\(_{364}\), and F\(_{367}\)) were reported in the receptor binding domain of the S-protein [45]. It’s also important to note that the S-protein was quite divergent between SARS-CoV and SARS-CoV-2; they shared only 76.47% amino acid identity [46]. Subsequently, it was found that although the SARS-CoV-2 and SARS-CoV uses the same cell receptor, Angiotensin-converting enzyme-2 (ACE-2) for entry into host cell, a single mutation (N\(_{6917}\)T) in the S-protein of SARS-CoV-2 significantly enhanced its binding affinity for ACE-2 [46,47].

Homologous and non-homologous recombination by strand switching ability of the RdRp is a unique ability of Coronaviruses [38]. Interesting recombination events were detected in the ORF-S of SARS-CoV, SARS-CoV-2 and SARS-like CoVs from bats (WIV1 and RsSHC014); two putative recombination breakpoints were detected at nucleotides 1,029 and 1,652, which separate the ORF-S of SARS-CoV-2 into three sub-regions [7]. This clearly depicts that S-protein of SARS-CoV-2 is actually a combination of bat SARS-CoV and an unknown betaCoV. Another report also supports the possibility of recombination in evolving the ORF-S of SARS-
CoV-2 [48]. However, further work is needed to test whether recombination has facilitated the latest pandemic emergence of SARS-CoV-2.

3. REPLICATION CYCLE OF THE CORONAVIRUS

3.1 Attachment and Entry

The viral S-protein plays a crucial role in the entry of SARS-CoV-2 into human host cells. The entry of SARS-CoV-2 into the host cell happens essentially through the interaction between the S-protein of the virus and the host ACE-2 receptors [49]. Another possible route of entry of the virus is through interaction of the viral S-protein with another human receptor called CD147 [50]. The interaction of the viral S-protein to the host receptor protein is mediated by a putative RBD which is present on the S1 subunit of the S-protein [33]. The amino acid residues present in the RBD of the viral S-protein, and the one in the human ACE-2 receptor have been worked out that are vital for the interaction. The amino acid present in the RBD of SARS-CoV-2 S-protein is a glutamine residue (Q\textsubscript{493}), and the amino acid present in the human ACE-2 receptor is a Lysine residue (K\textsubscript{313}) [47]. According to a recent report, the S-protein of SARS-CoV-2 binds to human ACE-2 receptor with 10-20 times higher efficiency that that of erstwhile SARS-CoV. This could possibly aid in explaining the observed higher infectivity of SARS-CoV-2 [51].

This interaction between the viral S-protein and the human ACE-2 receptor is the primary determinant of infection; this interaction also defines the tissue tropism of the virus. The human ACE-2 receptor is found in high abundance in human organs such as lung epithelia and the small intestine, which may give the plausible courses of passage for the virus [52]. In a single-cell RNA sequencing (scRNA-seq) study conducted recently with samples from human respiratory, cardiovascular, digestive, and urinary systems, it was found that ACE-2 protein exists in a relatively higher titre in the enterocytes of small intestine and the renal tubules, the alveolar epithelium cells of lung, the cardiocytes, the smooth muscle cells of the arteries and the gastrointestinal system [53]. This is a fitting explanation of higher vulnerability of organs such as lung, heart, oesophagus, kidney, bladder, and ileum to SARS-CoV-2.

After attachment, two proteolytic cleavages by host protease within the S2 subunit of the viral S-protein occur resulting in its activation [54]. Subsequently, the viral envelope gets fused with the host cell membrane via endocytosis [28], and finally the virus releases its genomic RNA into the host cell cytosol/cytoplasm (Fig. 2).

3.2 Replication and Transcription

Once inside the cell, the ORF-1\textsubscript{a} and ORF-1\textsubscript{ab} of the virion RNA is translated by host ribosomes to produce the viral replicative enzymes, polyprotein 1a/1ab (pp1a/pp1ab). A frame-shift between ORF-1\textsubscript{a} and ORF-1\textsubscript{b} initiates the production of both pp1a and pp1ab polypeptides which are processed by proteolysis for producing 16 Nsps. Assembly of these Nsps leads to formation of the replicate-transcriptase complex in the double-membrane vesicle to make a suitable environment for RNA synthesis [55-56]. Viral RNA synthesis generates genomic and sub-genomic RNAs through negative-strand intermediates by discontinuous transcription [57]. Sub-genomic RNAs serve as mRNAs for translation of the structural and other genes present downstream of the replicate polyprotein (Fig. 2).

3.3 Assembly and Release

The S, E, and M proteins enter the endoplasmic reticulum (ER) and Golgi apparatus assembly while the N-protein is attached with the genomic RNA. New virus particles are enveloped in the ERGIC; after assembly, the virus particles get transported via vesicles to the periphery and get released by exocytosis (Fig. 2).

4. IMMUNITY

SARS-CoV-2 infection can lead to the malfunction of lungs that show pneumonia-like symptoms. The two principal immunity mechanisms, innate and adaptive immunity, can act in response to the viral infection [46]. Innate immunity act as a primary antiviral defense mechanism necessary to combat against natural infection; but the insight of the specific innate immune response to SARS-CoV-2 is acutely narrow [58]. The T and B cells are lymphocytes forming a major part of the adaptive immune reaction in human. While the T-cells are responsible for the cell mediated immunity, the B-cells are important for humoral immunity [59]. The body’s humoral and innate immunity is stimulated by the presence of antigens, which, in turn, is mediated by virus-specific B- and T-cells [60]. Cytotoxic T-cells play crucial roles in cellular immunity during viral infection through the process of apoptosis. The CD4 T-cells allows the
B-cells for producing antibodies and strategize the feedback of other immune cells, whereas CD8 T-cells destroy the infected cells to lessen the viral drift. But down-regulated T-cell responses can be a consequence of immunopathology [58]. For CoV infections, it is of utmost importance to control the immune response, because an impaired immune response might result in immunopathological condition [60]. The disease severity might be dependent on the robustness of these T-cell responses. According to Li and co-workers [60], when the virus makes an entry into the cell, the antigen gets presented to the antigen-presentation cells, which happens to be the core part of the anti-viral immunity. B-cell response is a crucial memory response which can avert reinfection; nevertheless, SARS-CoV-2 draws out a vigorous B-cell response revealed by the rapid and near-universal detection of virus specific IgM, IgG, IgA and neutralizing IgG antibodies in the days following infection [58].

The SARS-specific IgG antibodies are generally S-protein and N-protein specific [17]. The N-protein and S-protein specific IgM and IgG are developed moderately after the symptom outbreak which can be used to diagnose viral infection; more precisely by studying the dynamics of S-specific IgG [61]. The findings of the kinetics of antibody response towards SARS-CoV-2 have been logically depicted [62]. Evidence of antibody feedback towards the SARS-CoV-2 infection revealed that individuals recovered from infection develop antibodies specific for the virus. However, infected individual might have a low level of neutralizing antibodies. Studies on coronaviruses like SARS-CoV and MERS-CoV suggested that the virus specific immune responses dwindle over time and provides partial protection from reinfection. As such, these details indicated that the immunity to SARS-CoV-2 might reduce after a primary infection; as a result, validated reports of naturally developed antibodies towards SARS-CoV-2 do not exist, yielding to the prophylactic characteristics observed in COVID-19 [58]. It can be mentioned that the cellular immunity may be scathing for recovery. It is yet to be revealed whether the existence of antibodies to SARS-CoV-2 renders immunity to its future infection in humans. Nevertheless, understanding the pathogenicity of the SARS-CoV-2 will provide various avenues to combat the virus but there are several urgent questions still remaining unanswered. Koch’s postulate has not been verified yet for the virus, which will give us the idea on the association and causative relationship between SARS-CoV-2 and COVID-19. The transmission routine of this virus among hosts is still unknown [63]. There is need of close monitoring to understand whether the virus continues evolving to become more virulent with time.

5. DIAGNOSIS

The clinical detection of SARS-CoV-2 infection is primarily based on auxiliary studies such as nucleic acid-based technology like real time quantitative polymerase chain reaction (RT-qPCR) and high throughput sequencing; serological tests like enzyme linked immunosorbent assay, immune identification technology of IgM/IgG; and computerized tomography-scan etc [60].

RT-qPCR is one of the most common and effective diagnostic technique to detect the presence of SARS-CoV-2 in the respiratory tract [64]. This test can be performed with the samples like sputum or nasopharyngeal swab and also on saliva. The upper respiratory tract, nasopharyngeal and oropharyngeal swabs are generally collected as specimen and sputum is considered as a non-invasive lower respiratory tract specimen [65]. Saliva is a more effective specimen considering the ease of sample collection; this can lessen the threat of hospital acquired infection. Due to the sudden outburst of COVID-19 cases, several private sector companies have started to rapidly produce RT-qPCR test kits for medical examination [60]. Besides, medical imaging like CT scans (especially, chest CT) can be performed which might show lesions in lung tissues of the infected individuals and is of considerable importance in early screening [66]. At times, RT-qPCR might provide inaccurate or false positive/negative results; in such cases, chest CT scan can be of assistance. Recently, reverse transcription-PCR (RT-PCR)-based rapid quick test kits were used for the diagnosis of SARS-CoV-2 infection, but it failed to give accurate results. For example, in Meghalaya, India, five suspected persons tested negative in their RT-PCR results whose samples were first tested positive with rapid testing kits (antibody test) [67]. According to a study, in patients with SARS-CoV and MERS-CoV infection, the chest-CT scans revealed ground glass opacities and consolidation, which has alike features to that of SARS-CoV-2 infection [68]. Since COVID-19 is a respiratory disease, CT scan might be helpful in recognizing distinguishable features in patients or individuals having a normal immune response [60].
Fig. 2. Life cycle of SARS-CoV-2. The S-protein binds to ACE-2 receptor of host cell and enters the cell through the S-protein facilitated the fusion of viral envelope with the host cell membrane. The virus releases its RNA into the cell which is then translated into viral replicase polyproteins pp1a and pp1ab; they are processed by viral proteases into 16 non-structural proteins (Nsps). Sub-genomic mRNAs are transcribed by polymerase and finally translated into corresponding viral proteins. Viral proteins and genome RNA are then assembled into virions in the RER and smooth walled Golgi vesicles, transported and released out of the cell via vesicles.

(S: spike; ACE-2: angiotensin-converting enzyme-2; Nsps: non-structural proteins; RER: rough endoplasmic reticulum; ERGIC: ER–Golgi intermediate compartment). The figure was adapted from the template provided by www.biorender.com

Although serological tests are not in routine use for diagnosis of SARS-CoV-2 infection and COVID-19, efforts are ongoing for standardization of some serological tests for the purpose. In such an effort, a comparison was made between IgM- and IgG-ELISA based on the S-protein and the N-protein based ELISA for diagnosis of SARS-CoV in 2005 itself. The N-protein based ELISA had shown a detection success rate 94.7% which was much higher the S-protein based ELISA in which detection success rate observed was only 58.9%. As such, the applicability of the N-protein based IgG ELISA was much higher than that of the S-protein based ELISA [69]. However, no such comparison has been reported yet in SARS-CoV-2.

The SHERLOCK (Specific High sensitivity Enzymatic Reporter unLOCKing) platform developed by Sherlock Biosciences, USA in 2019, uses the Cas13 endonuclease to detect specific genetic targets at low attomolar concentrations. The system works by isothermal amplification of RNA (or DNA with reverse transcriptase) employing recombinase polymerase amplification. A combination is made with the amplified nucleotides, the Cas13 endonuclease, the specific guide RNA for the target, a fluorophore-coupled short nucleotide sequence and a quencher. In presence of the target sequence among the amplified nucleotides, the Cas13 cleaves the RNA reporter activating the fluorophore which is finally detected [70].
6. THERAPEUTICS AND TREATMENT

The development of therapeutics for coronaviruses has been ongoing since the SARS-CoV outbreak in 2002-2003. Vaccines have been developed that were found effective in inducing synthesis of antibody and in providing protection against SARS-CoV. However, these vaccines were found to stimulate hypersensitivity to SARS-CoV components, posing risk for its application [73]. Till date, there are no antiviral drugs or vaccines in hand for the treatment of SARS-CoV-2. The recent COVID-19 outbreak has reemphasized the urgent need for treatment and preventive vaccine. Usually, for treatment of coronaviruses, three approaches are being employed [74]: (i) efficacy checking of most of the current antiviral drugs for drug repurposing, (ii) screening existing compounds listed in chemical libraries containing, (iii) discovery and development of new drugs specific to the present infection based on the genome and biophysical properties of SARS-CoV-2 [75]. Besides these, a variety of therapeutic approaches have been adopted which include monoclonal antibodies, angiotensin receptor blockers, nucleic acid-based therapy, epitope-based peptide vaccines etc. The therapeutics under trial are targeted for inhibition of entry, inhibition of viral fusion to the host cell membrane, inhibition of replication of viral genome by interferons, RNA interference mediated inhibition of replication, targeting viral proteases for inhibiting replication, and inhibition of replication by other compounds (Table 2) [76]. As of June, 2020, a variety of early-stage clinical research for developing COVID-19 therapeutic candidates has been taken up, some of which are mentioned below:

(i) antibodies (58 candidates)
(ii) antivirals (22 candidates)
(iii) cell-based compounds (14 candidates)
(iv) RNA-based compounds (5 candidates)
(v) screening of compounds/drugs to be repurposed (15 candidates)
(vi) other therapies, such as antimalarial, anti-inflammatory, antibiotics, interferon, protein-based, and receptor-modulating compounds (66 candidates) [77].

6.1 Prophylactic Options and Vaccines

The entry of viruses into the host cell which is the very first stage of the infection of coronaviruses, is mediated by a homo-trimeric form of highly glycosylated S-protein [78, 76]. The S-protein gets cleaved into two subunits (the S1- and S2-subunits) by proteolytic cleavages by host proteases, such as trypsin-33, factor Xa34 and cathepsin L35. The S1-subunit undergoes a conformational change to expose its RBD, especially its key residues involved in interaction (A475 and F486 in SARS-CoV-2), and interacts with human ACE-2 (hACE-2) receptor. The S2-subunit is primarily involved in subsequent fusion of the viral and host cell membranes that releases the viral RNA into the cytoplasm of the host cells.

From recovered SARS-CoV-2 patients in China, two monoclonal antibodies (mAbs) were isolated using SARS-CoV-2 RBD-specific memory-B cells. These antibodies could efficiently neutralize the S-protein of SARS-CoV-2; they were shown to specifically bind to the viral RBD, and to block its interaction with hACE-2 receptor [78-80]. Later, a recombinant protein fusing the extracellular domain of human ACE-2 and the Fc-region of the human immunoglobulin IgG1 was obtained and it was shown to exert inhibitory effect against SARS-CoV and SARS-CoV-2 by binding to the RBD of their S-proteins [81]. Another possible target to block CoV entry is to inhibit the transmembrane protease, serine-2
(TMPRSS2) which performs the proteolytic processing of the viral S-protein. This makes Camostat mesylate a potential candidate to gain efficient application and approval for clinical use; because it is known to inhibit TMPRSS2 [79]. Several clinical trials using the sera from convalescent SARS patients have also been reported to effectively neutralize SARS-CoV-2 entry. Therefore, this approach also carries some promise in treating SARS-CoV-2 infection [79].

The binding of the viral S-protein has been the main antigenic target to induce host immune responses against coronavirus infection. Serious consideration about vaccine development against this group of actually started seriously after the outbreaks of SARS and MERS. Several vaccine candidates have already been developed, but currently, most of them are in preclinical trial stages. The potential approaches for vaccine development include viral vector-based vaccines, DNA-based vaccines, subunit vaccines, vaccines based on virus like particles (VLPs), inactivated whole-virus vaccines and live attenuated vaccines [82]. Among them, the whole-virus vaccines have advantages such as their ability to stimulate toll-like receptors (TLRs) including TLR-3, TLR-7/8, and TLR-9, and having an inherent immunogenicity [82]. However, extensive testing is essential for such vaccines to confirm their safety. According to current reports, at present, Johnson & Johnson (USA) is one of the pioneer multinational companies working on developing vaccines against SARS-CoV-2; they have been using their proprietary Janssen AdVac® adenoviral vector and PER.C6® cell line technology for the purpose [83]. A recombinant live influenza vaccine, expressing SARS-CoV-2 proteins was recently developed by the University of Hong Kong [84]. Codagenix (USA) has been exploring their codon deoptimization technology for producing attenuated SARS-CoV-2 virions; such attenuated viruses could be finally used to develop SARS-CoV-2 vaccine [85]. Meanwhile, the recent advances in nanotechnology are being tried to be explored for developing vaccines against SARS-CoV-2. For example, a recombinant S-protein based virus-like nanoparticle, NVX-CoV2373, was developed by Novavax (USA); they found this nanoparticle to be sufficiently immunogenic [86]; they reported stimulation of high titre of neutralizing antibodies using their proprietary adjuvant called Matrix-M™. A subunit-based vaccine consisting of a trimerized version of SARS-CoV-2 S-protein using the patented Trimer-Tag® was reported to stimulate neutralizing antibodies against the virus in animal models; the technology is under development by Clover Biopharmaceuticals Technology (China) [87]. Meanwhile, another subunit-based vaccine comprising of only the RBD of SARS-CoV S-protein was developed by a group in Texas Children’s Hospital Center (USA) for Vaccine Development. This alum formulated vaccine was reported to have the advantage of having ability to minimize host immunopotentiation [88]. Recombinant adenovirus-based vaccine expressing the S-protein of MERS-CoV induced systemic responses providing long-lasting immunity against the virus upon intranasal administration in mice; therefore, this might be a potential vaccine candidate for clinical trial in case of SARS-CoV-2 as well [89]. Besides, using a recombinant parainfluenza virus type-3 vector (BHPIV3) expressing the MERS-CoV S-protein could also stimulate high level of SARS-CoV-neutralizing antibodies in the respiratory tract upon intranasal application; the antibody titre was only 2-fold less than natural infection [90]. The viral S-protein is the natural candidate for vaccine development against SARS-CoV-2 due to its ability to elicit neutralizing-antibodies and T-cell responses [91]. An efficient method to produce human mAbs against SARS-CoV from the memory B-cells was developed by Traggiai et al. [92]; their results highlighted the promises of human mAbs and ability of vaccines to elicit production of neutralizing antibodies. Human antibodies (such as single-chain antibodies) or humanized-nanobodies that can move across the membrane of the infected cells (called transbodies) and inhibit viral replication by interfering with virus proteins could also be potential candidate for vaccine development against SARS-CoV-2 [92].

Interferons (IFNs) constitute an important class of defense molecules and are known to inhibit viral replication and infection by inducing both innate and adaptive immune response. They have been another target for therapeutics against viral infections. Recombinant IFN-α was shown to be effective in treating SARS-patients in earlier clinical trials [93]. Earlier, in another set of clinical trials, administration of the IFN, alfacon along with a corticosteroid, showed to resolve 50% of lung abnormalities and to reduce impaired oxygen saturation associated with various respiratory diseases [93-94]. Furthermore, for elongated use, the intravenous immunoglobulin can be one of the safest immunomodulator among patients of all age groups. It inhibits
cytokine production and increases generation of anti-inflammatory mediators [95]. Meanwhile, for effective control of the diseases like SARS, thymosin α-1 (Ta-1) can be a potential immune booster [96]. Therefore, Ta 1 and intravenous immunoglobulin might also be considered as other promising alternative approaches to treat SARS-CoV-2 infection and/or COVID-19.

RNA-interference mediated gene silencing had become a promising tool of basic as well as applied research in recent times [97-98]. Gene silencing is achieved through cleavage and degradation of target RNAs using inducers called small interfering RNA (siRNA) that are complementary to the target RNAs. Several gene silencing approaches targeting key proteins of coronaviruses have shown promises to potential inhibit replication of SARS-CoV in Vero E6 cells [99]. In another approach of RNAi therapeutics against SARS-CoV, kidney FRhK4 cells of fetal rhesus monkey were transfected with siRNAs before or after viral infection. Prophylactic inhibitory effects were observed with up to 90% inhibition; and it lasted for at least 72 h. It was also observed that a combination of siRNA duplexes targeting different regions of the viral genome provided better inhibition of the infection of the target virus [100-101]. In another such trial, siRNAs targeting ACE-2 mRNA could effectively reduce viral infection in Vero E6 cell lines [102]. Moreover, siRNA-mediated knock down of actin-binding protein, ezrin, was also shown to provide protection against SARS infection in the entry stage [103].

In view of lack or absence of vaccines or specific drugs for severely infected patients of COVID-19, convalescent plasma therapy can prove to be an effective way to reduce the time-course of disease [104-105]. A study by Hung et al. [106] reported comparatively less risk of death of patients treated with convalescent plasma during the H1N1-virus pandemic in 2009, proving it to be one of the probable effective therapies against coronaviruses as well. It had been observed that in the acute phase of coronavirus-infection, the antibodies can limit viral reproduction helping in rapid recovery of the patients [107]. Convalescent plasma may help increasing the titres of neutralizing antibodies and this results in disappearance of SARS-CoV-2 RNA, finally leading to recovery [108]. However, a thorough study for the safety of SARS-CoV-2 specific plasma globulin products is essential.

### Table 2. Candidate drugs in use or in trial for treatment of infection of SARS-CoV-2

| Candidate drug                  | Description                  | Mode of action                                                                 |
|--------------------------------|------------------------------|-------------------------------------------------------------------------------|
| Remdesivir                     | antiviral                    | Adenosine nucleotide analog inhibiting RNA synthesis in coronaviruses [131]   |
| Hydroxychloroquine or chloroquine | antiparasitic and antirheumatic | Interferes with glycosylation of cellular receptors of SARS-CoV [115]       |
| Favipiravir                     | antiviral used against influenza | Inhibits the RNA-dependent RNA polymerase of RNA viruses [132]               |
| Lopinavir/ritonavir without or with Rebif | antiviral, immune suppression against influenza | A protease inhibitor; inhibits RNA replication and release of virus from host cell. Also inhibits the action of 3CL-protease [118] |
| Sarilumab                      | human monoclonal antibody against interleukin-6 receptor | Slows down the process of cytokine release, thus preventing organ damage [133] |
| ASC-09 + ritonavir              | antiviral                    | A protease inhibitor, inhibits RNA replication [134]                          |
| Tocilizumab                    | human monoclonal antibody against interleukin-6 receptor | Slows down the process of cytokine release, thus preventing organ damage [115] |
| Lenzilumab                     | humanized monoclonal antibody for relieving pneumonia | Acts against cytokine release syndrome [135]                                 |
| Dapagliflozin                  | sodium-glucose cotransporter 2 inhibitor | Prevents the lowering of cytosolic pH and reduces viral load [136]         |
| CD24Fc                         | antiviral immunomodulator against inflammatory response | Strengthens innate immune system against excessive inflammation [135]   |
Recently, an inactivated SARS-CoV-2 vaccine candidate PiCoVacc developed by Sinovacc Biotech Ltd (China) reported to induce neutralizing antibodies for 10 strains of SARS-CoV-2 when tested in animal models, thus proving it to be one of the most effective candidates for COVID-19 treatment [109]. A Massachusetts-based biotech company, Modern Inc. (USA), developed an RNA-based vaccine, mRNA-1273 targeting the S-protein of the virus; phase-1 trial of the vaccine was successful and phase-2 trial had been approved by the FDA (USA). Due to its potential, this candidate vaccine was granted a ‘fast track’ designation for phase-3 trial by July end [110].

6.2 Drugs and Others

The treatment of patients infected with SARS-CoV-2 is majorly symptomatic. Initially, combined administration of antiretroviral drugs such as lopinavir and ritonavir and others was reported to successfully suppress the virus and to improve immune response in patients [111]. The viral RdRp was realized to be a useful target of viral inhibitors, because, the enzyme was crucial for synthesis of viral RNA [111]. Being a known inhibitor of viral RdRp, remdesivir, an adenosine triphosphate analog, is as an effective drug against all RNA viruses that prevents the viral replication [112]. Therefore, remdesivir has been the most widely used drug against SARS-CoV-2 infection as well till now. Preliminary data on administration of remdesivir on patients with severe COVID-19 symptoms showed quicker recovery compared to other therapies. In in vitro experiments too, remdesivir was found to effectively control SARS-CoV-2 [13]. Owing to these success, the drug gained authorization for emergency use from the FDA on May 1, 2020 [113]. Meanwhile, the antimalarial drug, chloroquine, was also found to exhibit immunomodulatory activity, and to inhibit SARS-CoV-2 effectively in vitro [13]. Therefore, there was wide speculation on its prophylactic use against SARS-CoV-2 infection; however, WHO had waned against its regular use due to its side-effects and lack of sufficient evidence of its effectiveness in suppressing SARS-CoV-2 infection [114]. Nevertheless, chloroquine and hydroxychloroquine were found to inhibit the viral entry by blocking the autophagosome and lysosomal fusion, which is possibly the sole route of entry of the SARS-CoV-2. In clinically controlled trial, the drugs also could inhibit the viral genome replication [115]. Meanwhile, cell experiment with arbidol, a small indole derivative, was also found to show antiviral effect against SARS-CoV [116]; it works by negatively targeting the interaction between the viral S-protein and the host ACE-2 receptor thus inhibiting the membrane fusion, and could significantly reduce the incidence of severe cases of COVID-19 [115-116]. The use of nucleoside analogues as antivirals was also perceived to be another approach for treatment against SARS-CoV-2 infection [117]; diverse classes of nucleoside analogues were earlier used in Vero cells against SARS-CoV [118]. Similarly, in adult patients severely infected with MERS-CoV, a guanosine analogue called ribavirin, administered in combination with interferon-α2a showed significantly better survival rate in 2014 [119]. Therefore, ribavirin was also taken for potential repurposing for treatment of COVID-19 patients. Other nucleoside analogues, such as neuraminidase inhibitors and peptide EK1, also showed potential to be used for the treatment of SARS-CoV-2 infection [74]. Nevertheless, targeting the main viral protease, i.e., the viral 3CLpro has been the main focus of most of the current computational and experimental research aimed at drug development against SARS-CoV-2 infection. In this line, an antineoplastic drug, carmofur, was reported to successfully inhibit the 3CLpro of SARS-CoV-2, and to prevent viral perpetuation in host cells [120]. In another study, favipiravir, another anti-viral drug, was also reported to efficiently suppressing SARS-CoV-2 infection with fewer side effects. These findings were reported from a clinical trial on 70 patient-volunteers in Shenzhen in Guangdong province of China; and the drug was approved for use by the National Medical Products Administration of China [121].

Recently, a CRISPR-based system has been proposed to be used against SARS-CoV-2 infection and COVID-19; this system recognizes and thereby degrades the viral genome in the host’s cells [122]. The technique employs a novel RNA-guided RNA endonuclease, a class-2 type VI-D CRISPR-Cas13d system which has high catalytic activity in human. The entire system was derived from Ruminococcus flavefaciens XPD3002, and was previously shown to efficiently inhibit the entry of other RNA viruses into human cells [123-124].

It has been previously mentioned (section 2.3) that the E-protein of SARS-CoV-2 has an important role in viral morphogenesis, particularly, during viral assembly. Therefore, it could also be another target for controlling the
infection of the virus. It was shown that hexamethylene amidorlide, a pyrazine amidorlide, generally used against HIV, could also successfully block this SARS-CoV-2 E-protein-associated ion channel activity in the mammalian cells [125].

One of the most recent developments about the treatment of SARS-CoV-2 infection is the repurposing of favipiravir, which is a common viral RNA polymerase inhibitor. The drug, which is a pyrazinecarboxamid compound, is primarily used against influenza in different countries. Currently, Japan and USA have been conducting phase-2 and phase-3 trials, respectively, of this drug to test its effectiveness against SARS-CoV-2 infection [126-127]. Very recently, Glenmark Pharmaceuticals, India had reported clinical evidence of favipiravir successfully decreasing viral loads in COVID-19 patients of very wide age group (20 to above 90 years) within only four days. Upto 88% improvement in symptoms in patients having mild to moderate symptoms was reported in those trials. The firm was subsequently awarded with regulatory approval of production and marketing of the drug in the country [128].

There also had been trial of Indian traditional ayurvedic herbs for COVID-19. Herbs used in the treatment of malaria; Ashwagandha, Yashtimadhu (Mulethi), Guduchi Pippali (Giloy) and a polyherbal Ayurvedic formulation, called AYUSH-64, have been identified as the four candidates. Another Ayurvedic formulation developed by Pankajakasthuri Herbal Research Foundation from Kerala province, India has been cleared for clinical trials on COVID-19 infected adults by Clinical Trials Registry of India. It was reported that it has proved to be quite successful in the clinical trials in reducing COVID-19 symptoms [129]. There are still a number of clinical trials going on in Indian and other countries for finding a successful therapy/drug against the SARS-CoV-2 disease.

The most recent development in the therapeutic against SARS-CoV-2 is a known steroid called dexamethasone. In a large scale trial in UK, it had been successful in reducing the death rate in SARS-CoV-2 infected patients under both ventilated and non-ventilated conditions [130].

7. CONCLUSION

It’s already nearly seven months since the first report of the SARS-CoV-2 infection. The COVID-19 pandemic had caught the planet unprepared and the disease is yet to come under complete control of the existing healthcare system. Although China has started nearly all usual economic activities, there have been reports of SARS-CoV-2 positive cases coming in regular intervals. Same is the case in Europe; although it is widely perceived that peak infection is over, it is unpredictable what will happen after normalcy returns. In countries like USA, India, Brazil, Pakistan etc, the infection rate is gradually increasing and the peak is possibly not near yet. There are some predictions that the situation actually may worsen during the coming winter. The healthcare system has almost collapsed in several countries and as of now, the major emphasis is on flattening the curve. There is almost no provision at this point to fill the gaps in understanding the epidemiology of the disease, and the mechanism of evolution and mode of infection of the virus. There are several questions, remaining unanswered about the pandemic that are keys in development of the vaccine and therapeutics. Individual countries mobilising ample funding for needed research in this line is a challenge; therefore, a concerted effort should have been the aim of the scientific community. However, recent socio-political developments are obstructing the creation of such wilful and dependable consortium. We believe, the conscience of the world leaders and policymakers will eventually collate and humankind will prevail over the virus; the sooner, the better.

ACKNOWLEDGEMENTS

RG is grateful to Prof BK Sarmah for mentoring. RRP acknowledges research fellowship from DBT (Twinning) project (Grant No: BT/PR25287/NER/95/1113/2017; 01/08/2018). Research in BKB lab is supported by DBT, DST and ICAR (all three are Govt. of India agencies).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/59040