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A review on microbial strains and their metabolites used against SARS viruses and their mode of action

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Abstract
Microbes and their strains have made a phenomenal contribution in the well-being of people throughout the world. This has led to positive contribution towards the health and different illness in people. These microbes add by producing many primary and secondary metabolites, which are capable of reducing the affect of various infection and pandemic that has caused adverse effect in different places at different point of time. The sudden outbreak of Coronavirus SARS CoV-2 disease and its rapid spread to all over the world has alarmed the medical science mainly due to its lethal nature. Particular therapy for SARS virus infection is not yet available although, current clinical trials have been rapidly initiated after the recent outbreak. This review focus on different microbial strains and their metabolites that are used against different SARS viruses that are known to cause Acute Respiratory Syndrome in human.

Keywords: SARS virus, microbores, metabolites, mode of action

Introduction
Severe Acute Respiratory Syndrome (SARS)- related coronavirus is a virus originated from zoonotic origin in the early 2000 in some ranges of China, leading to a severe respiratory tract infection. The virus is known to cause infections in both humans and animals including bats and certain other mammals. It is a highly communicable, serious and potentially life intimidating form of pneumonia. This strain was first identified in 2003 by the Chinese scientist and was named as SARS-CoV. The virus was thought to be an animal virus from an uncertain animal reservoir, perhaps the bats and chivet cats and due to mutation, the virus enables itself to infect humans. The first case of SARS-CoV was found in the year 2002 in the Guangdong provinces of China. During studies, it was found that the person was infected through animal- to- human transmission.
The virus turn out to be an epidemic, affecting almost 26 countries with more than 8000 cases till the mid of 2003 by human to human transmission method occurred due to the absence of adequate health precautions. During the period of infection there were 8098 reported cases of SARS and 774 deaths (WHO report). People at their elderly age i.e., around 65 are mostly at risk since, out of all those who died, half of those are found to be in this group. This pandemic was eventually brought under control in July 2003. As per the report of May 24, 2020; 23;43 IST by COVID-19 live tracker there is 1,38,536 conform cases of COVID-19 with 76, 811 active cases, 57,692 and 4,024 deceased cases in India (https://covid19-indialive.easocare.com/).

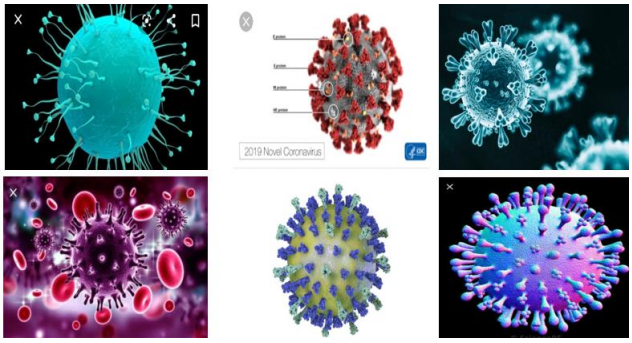

Fig 1: Images of different SARS viruses (*top line, left to right*: NIPAH, 2019 Novel Coronavirus, Novel Coronavirus *bottom line,left to right*: HIV-AIDS, MERS, Avian flu virus (Source: Google search)

The different types and strains of SARS include, MERS, NIPAH, Influenza, SARS-CoV, Bird flu, etc. All the viral outbreaks under SARS virus shows the common flu- like symptoms that usually shows up between 2 to 14 days after infection (Fig. 1). Sometimes, the time between coming in contact with the virus and the incubation period (start of symptoms) can be more than 14 days. The symptoms include, high fever, headaches, diarrhoea, muscle pain, etc. and the further infection will affect our lungs and airways. During this period, the infected person experiences a dry cough and difficulty in breathing that will lead to an increasing lack of oxygen in the blood which can be fatal. SARS virus has high potential for natural evolution.

SARS is found to be a very contagious form of pneumonia which is currently treated by, assisting with breathing using a ventilator to deliver oxygen, antibiotics to treat bacteria, antiviral medications, high doses of steroids to reduce swelling in the lungs.

The SARS virus tends to spread when people are in proximity and travels through droplets in the air released by coughing and sneezing of an infected person. Currently, there is no specific medication for SARS however; further research is going on to discover a vaccine. Scientists are carrying on their research using different chemicals including chloroquine, hydroxychloroquine, remdesivir, lopinavir; ritonavir, etc. to minimize the affect of the virus to some extent. Different microbial strains and metabolites are being used by the researcher to control or fight against the very crucial SARS virus which is creating a great concern among the people in present situation, that will be discussed further.

Mode of action of sars viruses

The SARS viruses have spikes containing glycoprotein that must bind to a molecule on the cell surface of the host in order to infect a host cell. These viruses are generally species specific. Certain species have receptors through which the viruses bind to the host cell. It can be said that, no binding= no infection. Host jumping is usually triggered by mutation in spike protein which change and allow the spike to bind to a new species. To enter the human cells, coronaviruses are seen to use the same receptor as SARS coronavirus, and that receptor is known to be Angiotensin- converting enzyme 2 (ACE2).

Infections usually start with the cells of the respiratory mucosa and then proceed to the epithelial cells and alveoli in lungs. Binding of receptor is accompanied by the fusion of the viral membrane with the host membrane where the release of nuclear capsid into the cell takes place (Fig. 3). Through the host machinery, the virus then replicates producing RNA releasing proteins. These are then assembled together to form new viral particles called virions. As the new virions are released, the host cell dies. Uncontrolled cause of the virus destroys respiratory tissues and starts producing symptoms.

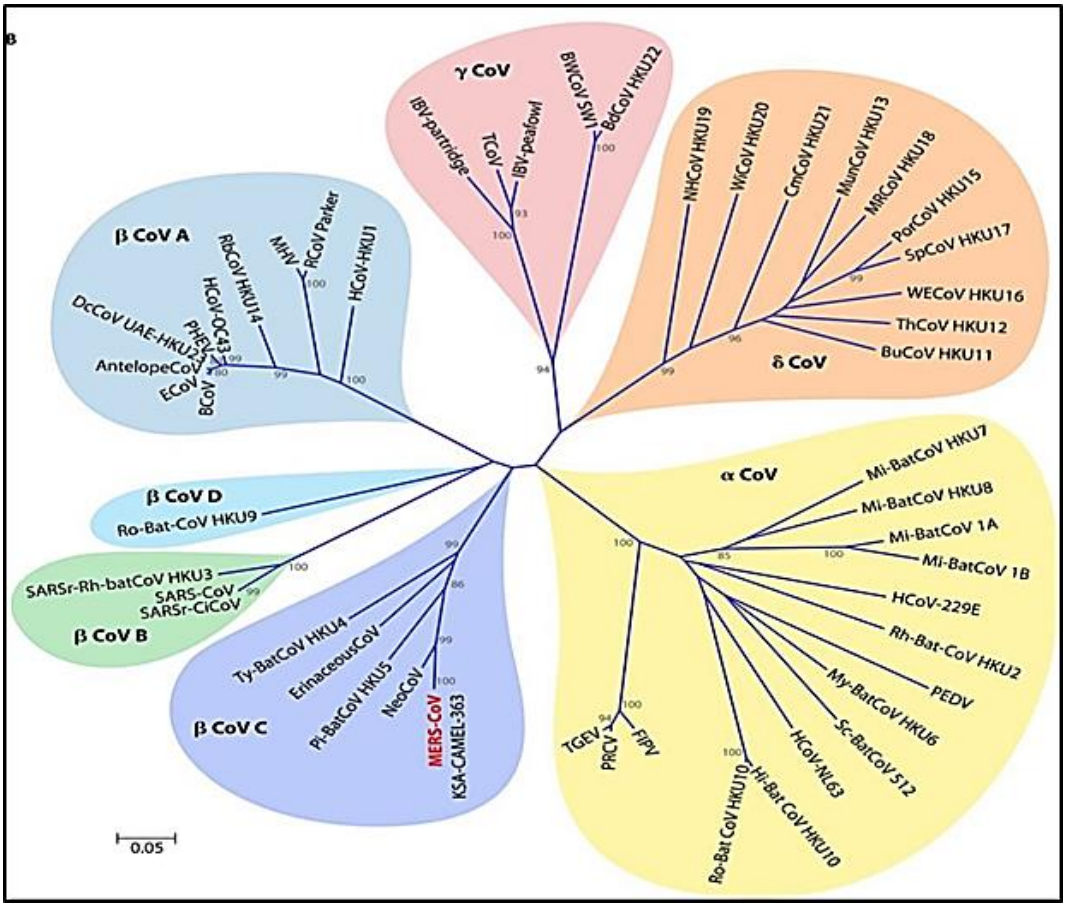

Fig 2: Taxonomy of Coronaviridae according to the International Committee on Taxonomy of Viruses (Source: Jasper *et al*., 2015) [9]

Different microbial strains and their metabolites used against sars viruses and their mode of action

Lactic acid bacteria used against Influenza A

Influenza A is a negative sense, single stranded, enveloped, segmented RNA virus that infect the epithelial cells of the upper and lower respiratory tract which include the trachea, lungs and the nasal mucosa too. Once the influenza virus enters the host body, the innate immunity is activated and the interferons are secreted by the host cell to minimize the early viral proliferation, then the adaptive immunity is activated by

the cytokines produce during viral infection. Many studies have shown that, the antiviral protective effects of a heat-killed strain of lactic acid bacteria, *Lactobacillus casei* DK 128, a promising probiotic isolated from fermented vegetables, on Influenza viruses.

Lactic acid bacteria, commonly used in the form of probiotics that helps to improve digestive health that leads to offer the protection against different subtypes of Influenza A virus, that results in reduced weight loss after virus infection and lower amounts of virus replication in the lungs according to a study led by Georgia State University. (Miyazaki, T., 2017)

Availability of lactic acid bacteria in food have been noted such as fermented vegetables and dairy products contain a variety of this bacteria and holds a number of health benefits in addition to being used as probiotics. Other foods rich in lactic acid bacteria include fermented cereal, yogurt, sourdough bread and bread- like products, fermented milk (cheeses, yogurt, curd, etc.).

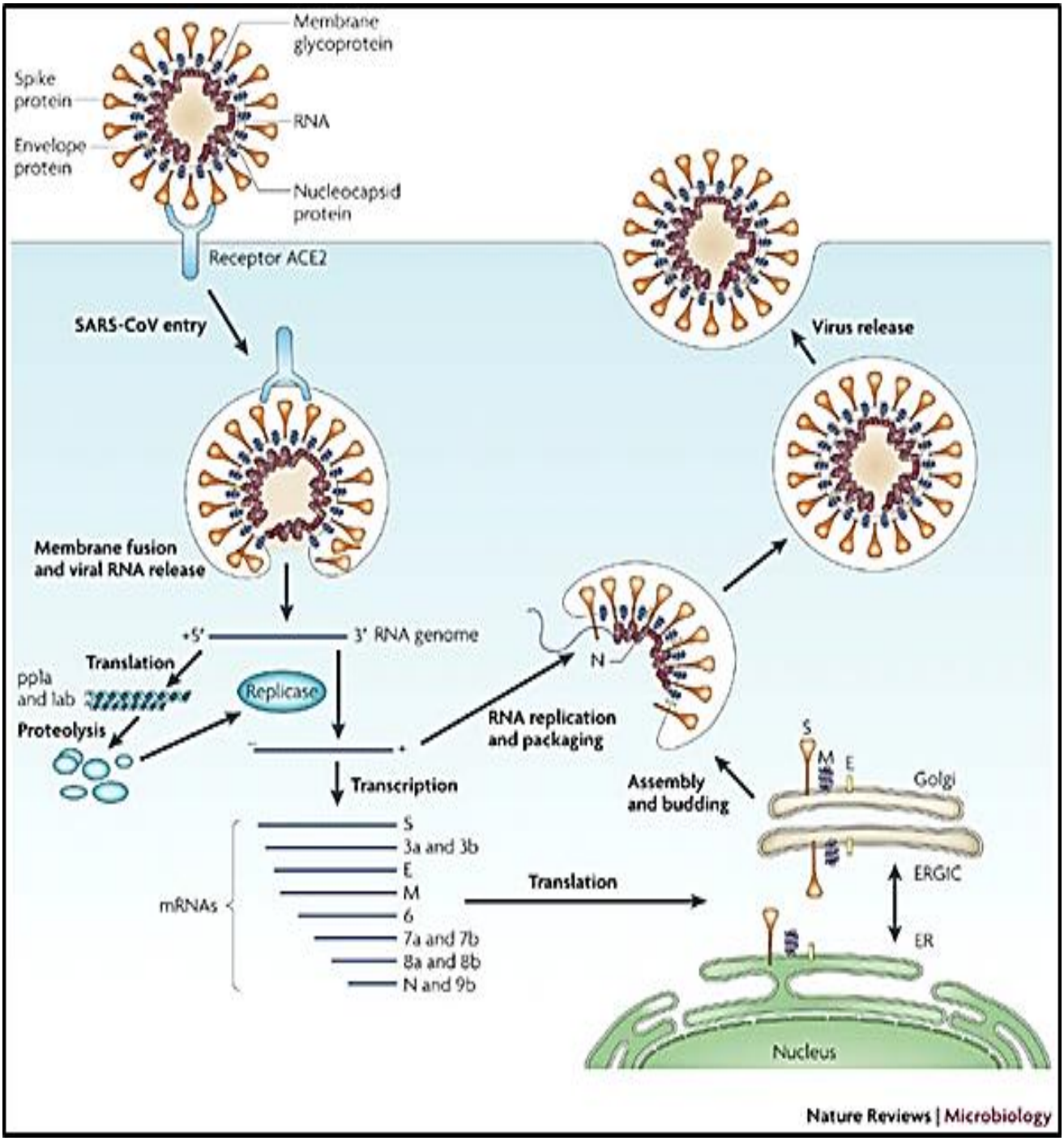

Fig 3: Life cycle of SARS virus in the host cell (Source: Du *et al*., 2009) [1]

Yeast surface- displayed H5N1 avian influenza vaccines

Avian flu or birds flu is a zoonotic influenza virus that is basically found in birds. Human infection was not stated earlier but due to some genetical changes in the strains of the virus, it has started showing symptoms in human body itself. The majority of the human cases suffering has been associated with direct or indirect contact with infected or live birds.

So, a rapid vaccine production against this pandemic threat is desired. It is reported that herein, a paradigm- shift influenza vaccine technology by presenting H5N1 hemagglutinin (HA) to the surface of yeast (Fig. 4). It was demonstrated for the

first time, that the hemagglutinin surface- presented yeast can be used as influenza vaccines to elicit both humoral and cell mediated immunity in the mice (Lei *et al*., 2016) [11]

A high level of H5N1 HA- specific I_gG2a antibody production was detected after boost immunization. Further, it was demonstrated that the yeast surface- displayed hemagglutinin preserves its antigenic sites and it binds to both avian- and human- type receptors. The vaccine was found to exhibit high cross- reactivity to both homologous and heterologous H5N1 viruses. A high level production of anti- HA antibodies was detected in the mice five months after vaccination. The result of the experiment indicated that, the yeast vaccine offered complete protection in mice from lethal H5N1 virus.

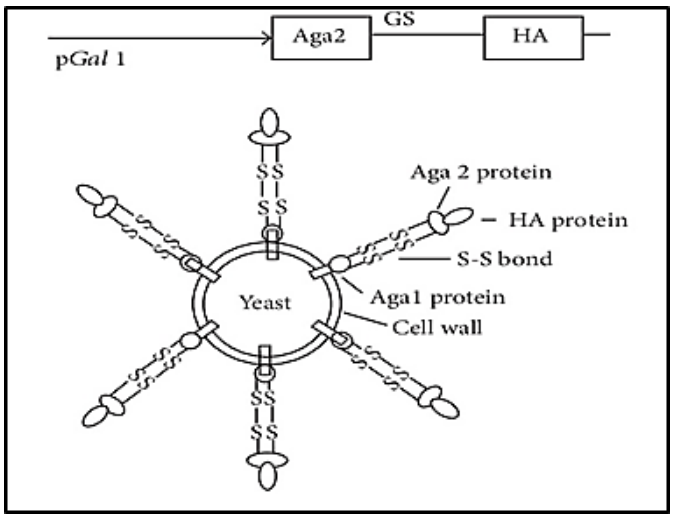

Fig 4: Yeast surface- displayed H5N1 Avian Influenza vaccines (Source: Lei *et al*., 2016) [11]

Use of antibiotics to prevent HIV

A combination of the antibiotics atobvaquone and azythromycin is at least effective and safe at preventing serious bacterial infections in HIV positive children.

It is found that, cotrimoxazole is an effective prophylactic against PCP pneumonia in HIV- positive individuals. The antibiotic is also used in a broad spectrum across the world in HIV- positive individuals (Carter, M., 2004)

Lactic acid bacteria used against HIV

Transmission of Human Immunodeficiency Virus (HIV) from mother to the infant during breastfeeding period is a marked source of new pediatric HIV-1 infections worldwide.

However, most breastfed infants remain uninfected. Natural defenses in the infants that confers protection against the transmission of HIV-1 from the mother to child was recognized and revealed the protective benefits of breastfeeding.

Lactic acid bacteria were isolated from the breast milk of healthy women for the ability to inhibit HIV-1 infection in vitro. A total of 38 strains of breast milk bacteria belonging to 15 different species were evaluated. Significant inhibition of R5- tropic HIV-1 was demonstrated using heat- killed bacteria, most markedly among breast milk strains of *Lactobacillus* and *Pediococcus* (Martin *et al*., 2010) [13]

Sheep helping to fight against SARS coronavirus

At the University of Dundee, an experiment was carried out. They identified 28 proteins created by SARS-CoV2 that produce an immune response in the body. These proteins are considered to be the vital research tools for developing diagnostics.

Viruses are encoded by genetic information called RNA. In the first step, the genetic sequence of the virus was taken and converted it to DNA and amplified the genetic material many millions of times by using the process PCR (Polymerase Chain Reaction). The sequence is then used to program bacteria to make the proteins that make up the virus, enabling the scientists to harvest and prepare them in large amounts.

These proteins are then introduced into sheep on a local farm and the sheep start to produce antibodies against viral proteins that can be harvested from them every few weeks.

The antibodies are then brought back to the laboratories in Dundee and are prepared for their various uses. The final product will be sent to labs around the world which will help in the fight against COVID-19.

These antibodies bind very tightly to the viral proteins and do not recognize other proteins. Each antibody will only fit the viral protein, it was designed for. This is helpful in identifying each part of the virus as well as the complete virus and identifies the mechanism of infection in human. (Davies, P., 2020)

Conclusion

SARS and it's related strains which are the cause of various pandemic outbreak since late 20s, the most recent and the latest outbreak is COVID-19 (SARS-COV2) which is creating a mess all over the world right now. This disease is mostly of zoonotic origin is a deadly new infectious disease with its ability to spread from person to person, country to country and can spread all over the world in just a blink of an eye like the recent spread of COVID-19 from a small town of China, Wuhan to almost 23 countries under its effect till date. Despite of the rapid spread of the virus world wide, different control measures are suggested by WHO and various research organisations to minimize the pandemic outbreak.

Since the SARS cause a non-specific clinical illness, there need a rapid diagnosis and control in the disease. In such situations understanding the risk and good communication practice is the key element in the management of the subsequent outcomes.

Due to the absence of effective drug or vaccine against SARS virus, control of this pandemic relies on the rapid identification of cases and their appropriate management which include isolation of the suspect, personal hygiene. This simple step taken by every individual might help in some extent to prevent the spreading of the disease to others.

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