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COVID-19 Evolution and Alternative Medicine - A Review

Shubhangi Goel[1] and **Anjana Goel**[2]*

[1]King George's Medical University, Lucknow - 226 001, Uttar Pradesh India. [2]GLA University, Mathura - 281 406, Uttar Pradesh, India

Abstract

The current global health emergency, COVID-19, is not the first time that coronaviruses have posed a threat to human world shrinking our numbers by thousands. Before this SARS-CoV in 2003 and MERS-CoV in 2013 have caused epidemics. Four months in existence, and it has already affected 1,995,983 people and taken over 131,037 lives worldwide, yet we do not have any specific treatment available with us and the management is purely empirical. Looking at the similarities between SARS-CoV and SARS-CoV-2 in origin, genomics, pathogenesis and epidemiology, we can bring the researches done for SARS-CoV in use which can be our guide in finding an effective management strategy against SARS-CoV-2. There are various researches and studies reporting the use and effect of various phytochemical compounds in SARS-CoV treatment. Already, the thought has been put into action and in-silico screening for various natural plant compounds have been done to find a potential candidate compound. One such example is of curcumin, a secondary metabolite of turmeric, which is found to be effective against COVID-19 protease by molecular docking analysis.

Keywords: Coronavirus, SARS-CoV, Herbal medicine, Complementary medicine

***Correspondence:** anjana.goel@gla.ac.in; +91-9897006326

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INTRODUCTION

Coronaviruses are well known pathogenic organisms of humans and animals which cause a broad spectrum of respiratory, gastrointestinal, neurological and systemic diseases[1].

Deriving its name from the word 'corona'[2] meaning outer fringe(because of the presence of spiky outer enveloped protein coat), coronaviruses belong to the family Coronaviridae which are further subdivided into four genera namely, Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus[3].

Evolution of Covid-19

The genera Alphacoronaviruses and Betacoronaviruses contain viruses infecting both humans and animals (Table 1)[4,5] while the genus *Gammacoronavirus* and Deltacoronavirus contains viruses specifically infecting animals (Table 2)[4]; the first one being seen in whales and birds, and the latter ones are isolated from pigs and birds[4].

Discovered in early 1930's as a pathogen causing mild respiratory infection in domesticated chickens[1] coronaviruses gained major attention in 2003 after the emergence of SARS(Severe Acute Respiratory Virus) which caused a major global epidemic wiping out thousands of global population.

Before 2003 epidemic was inked in the history of humankind, coronaviruses were known to cause mild respiratory infections. It was the first time, when coronaviruses were seen posing such a serious threat. This was a game-changing event which led to various researches. As reported, SARS was known to be caused by cross species transmission- from bats to humans.

Since then, coronaviruses are seemingly undergoing variety of mutations and leaping into humans causing infections, both mild and severe. After SARS, four more strains of coronaviruses have been recognised till now of which two strains namely, HCoV HKU-1 and NL63 are known to cause mild respiratory disease while two strains namely, MERS-CoV and SARS-CoV-2 have caused epidemics affecting human population in large numbers and

Table 1. Recognised strains of Coronavirus affecting humans

Alphacoronavirus	HCoV- 229E
	HCoV-NL63
Betacoronavirus	HCoV-OC43
	HCoV-HKU1
	SARS-CoV
	MERS-CoV
	SARS-CoV-2

Table 2. Recognised strains of Coronavirus affecting animals

Alphacoronavirus	Mi-BatCoV-HKU7
	Mi-BatCoV-HKU8
	Mi-BatCoV-1A
	Mi-BatCoV-1B
	Rh-BatCoV-HKU2
	PEDV
	My-BatCoV-HKU6
	Sc-BatCoV-512
	Hi-BatCoV-HKU10
	Ro-BatCov-HKU10
	TGEV
	FIPV
	PRCV
Betacoronavirus	
β-CoV A	RCoV Parker
	MHV
	RbCoV HKU14
	Antelope CoV
	B CoV
	E CoV
	PHEV
	DcCoV-UAE-HKU23
β-CoV B	SARSr-Rh batCoV-HKU3
	SARSr-CiCoV
β-CoV C	Erinaceous CoV
	MERS-CoV
	Neo-CoV
	Ty-batCoV-HKU4
	Pi-BatCoV-HKU5
	KSA-Camel-363
β-CoV D	Ro-Bat-CoV-HKU9
γ-CoV	IBV-partridge
	TCoV
	IBV-peafowl
	BdCoV-HKU22
	BWCoV-SW1
δ-CoV	NHCoV HKU19
	WiCoV HKU20
	CmCoV HKU21
	MunCoV HKU13
	MRCoV HKU18
	PorCoV HKU15
	SpCoV HKU17
	WECoV HKU16
	ThCoV HKU12
	BuCoV HKU11

severity[1]. All the seven strains of coronaviruses recognised in humans are known to jump to humans from animals crossing species barrier (Fig. 1). The progenitor viruses of the recognised strains are seen in different host animals. HCoV-NL63, HCoV-229E, MERS- CoV and SARS- CoV are considered to have their origin in bats while HCoV-HKU1 and HCoV-OC43 are most likely to be originated from rodents[3,6,7]. Domesticated animals may play important roles as intermediate hosts which enable transmission of these viruses from their natural hosts to humans. SARS-CoV finds its intermediate hosts in civets[3,8,9], HCoV-229E in camelids while MERS-CoV most likely found its way to humans through dromedary camels[3,10].

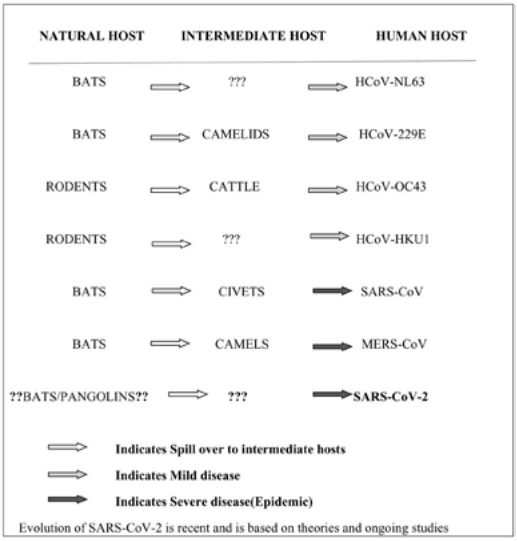

Fig. 1. Evolution of various strains of recognised human coronavirus from natural to human host

The latest recently recognised strain of all, SARS-CoV-2, was recognised in December 2019, in Wuhan city of China. Seeing its genomic similarity with SARS-CoV, it is thought to have paved its way to humans from animals through the live animal markets of China. The two probable theories of the origin of the virus gives bats[11-13] or pangolins[13, 4] as the natural host of the virus, bats being the most closest. The virus, likely, then mutated and evolved to spread most probably though an intermediate animal bridge to humans and now human to human transmission can be easily noted.

Being of the common origin as of SARS-CoV, it was hypothesized that the virulence of SARS-CoV-2 will also be affected by the increasing temperatures especially above 39°C (same as in case of SARS-CoV). According to the various studies conducted in this regard, the result remains inconclusive. According to a study conducted in China, COVID-19 mortality decreased with increase in ambient temperature (above 39°C) along with increased absolute humidity[15]. A study conducted by Wang *et al.*[16] showed reduction in transmission of the disease while studies conducted by Ye Tao *et al.*[17] and Zhu *et al.*[18] showed ambient temperature had no effect on the transmission of SARS-CoV-2.

Complementary Medicine

Since the emergence of human race, plants have been the source of countless compounds having medicinal properties and lead to drug discovery. Since the ancient times, Indian Ayurveda, Traditional Chinese Medicine Literature, ancient Egyptian Ebers Papyrus all gives description of various plants and herbs having medicinal properties which are even today used all over the world for various health benefits. Different plant compounds act as immune boosters and can act as antibacterials, antivirals as well as antifungals. The coronaviruses encodes various proteins which enables its functioning. Many plants produce compounds interfere with these proteins and can become a target for drug development. Since the gene sequence of COVID-19 has very high similarities between the man proteins of COVID-19 and in SARS or MERS, thus previously reported anti-SARS or anti-MERS natural compounds may become a valuable guide to find the affective anti-COVID-19 herbal plants (Table 3).

There are more than a dozen of proteins which are encoded by coronavirus. Some of these proteins are essential to viral entry and replication. Papain-like protease (PLpro), 3C-like protease (3CLpro) and spike protein are the well studied proteins so far. All of these three proteins make attractive targets for drug development. Some of the herbal plants have been screened in silico by Narges & Neda 2020 to find the inhibitors for COVID-19 proteases, which could be an effective strategy for combating against this deadly virus. Due to the strong interaction of these natural compounds with enzymatically conserved regions and specific functionality, these compounds can be considered as effective antiviral drugs due to their natural origin and less likely to produce

Table 3. Plant products effective against various strains of Human Coronavirus

Virus	Plant/Plant Product	Mode Of Action	Reference
SARS-CoV	Phenolic plant compounds and Extract of roots of Isatis indigotica	Inhibits SARS-3CLpro enzyme activity	[28,29]
	Flavanoid Baicalin from Scutellaria baicalensis	Inhibits Angiotensin Converting Enzyme	[30,31,32]
	Water extract of Houttuynia cordata	Inhibit the activity of viral SARS-3 CLpro Block viral RNA-dependent RNA polymerase activity	[32,33,34]
	Glycyrhizzin from the liquorice roots	Affects various cellular signalling pathways	[35,36,37]
	Mannose-specific plant lectins derived from Galanthus nivalis, Hippeastrum hybrid and Allium porrum	Inhibition of virus replication at an early stage by blocking S- receptor interaction	[35, 38, 39]
	Reserpine derived from various species of Rauwolfia	Inhibits replication of SARS-CoV	[35, 40]
	Scutellarein and myricetin	Inhibit nsP13 helicase by affecting the ATPase activity	[32,41]
	Escin from horsechestnut		[35, 42]
	Extracts of Rheum palmatum	Inhibit SARS-3CLpro activity	[32, 43]
	Flavonoids (herbacetin, pectolinarin, epigallocatechin gallate, rhoifolin, quercetin, and gallocatechin gallate)	Inhibit SARS-3CLpro activity	[32, 44, 45, 46]
	Quercetin and TSL-1 from leaves of Toona sinensis Roem	Inhibit the cellular entry of SARS-CoV	[32, 47]
	Emodin derived from genus Rheum and Polygonum	Inhibits interaction of SARS-CoV s pike protein and ACE2 Blocks 3a ion channel inhibiting SARS-CoV triggered apoptosis	[32, 48, 49]
	Tetra-O-galloyl-β-D-glucose from Galla chinensis	Binds with surface spike protein thus interrupting with membrane fusion of SARS-CoV	[32, 50]
	Luteolin from Veronicalina riifolia	Binds with surface spike protein thus interrupting with membrane fusion of SARS-CoV	[32, 50]
	Lycorine extracted from Lycoris radiate	Unclear	[51]
	Ginsenoside-Rb1 from Panax ginseng	-	[40]
	Biflavonoids (Amentoflavone, apigenin, quercetin,luteolin) from Torreya nucifera	Inhibits SARS-CoV 3CL pro activity	[52]
	Kaempferol derivatives	Interfers with 3a ion channel of SARS CoV	[32, 53]
	Dieckol from edible brown algae Ecklonia cava	Inhibits SARS-CoV 3CLpro activity	[54]
MERS-CoV	Herbacetin, quercetin, isobavaschalcone, 3-β-D glucoside and helichrysetin	Inhibits cleavage activity of 3CLpro enzyme	[32, 55]
HCoV-229E	Saikosaponins A,B2,C,D (from Bupleurum spp., Heteromorpha spp., Scrophularia scorodonia)	Inhibits viral attachment and penetration at an early stage (saikosaponin B2)	[29, 56]
HCoV-OC43	Tetrandrine, fangchinolif ne, and cepharanthine	Inhibit the expression of HCoV- OC43 spike and nucleocapsid protein. Immunomodulation	[32, 57, 58]
	Emodin derived from genus Rheum and Polygonum	Blocks 3a ion channel inhibiting HCoV-OC43 triggered apoptosis	[32,49, 49]

Table 4. Commonly used Allopathic Medicines in COVID-19

Drug	Initial Use	Mechanism of Action	Side Effects	References
Remdesivir	Ebola virus Inhibits viral RNA	Kidney injury polymerase	[21, 23, 59]	
Lopinavir	Anti HIV	Acts against viral 3CL protease	Gastrointestinal intolerance, Pancreatitis, cardiac conduction abnormalities, hepatotoxicity	[21,23, 60]
Chloroquine	Anti malarial	Decrease Lysosomal autophagy preventing entry of virus	Abdominal cramps,anorexia, diarrhea,nausea, vomiting. Cardiovascular effects (QTc prolongation), hematologic effects (including hemolysis with G6PD deficiency), hypoglycemia, retinal toxicity, neuropsychiatric and central nervous system effects, idiosyncratic adverse drug reactions	[21, 23, 61]
Interferon beta-1a	Treatment of Multiple Sclerosis	Interfere with viral replication and up regulates CD73 in pulmonary endothelial cells	injection site reactions, flu-like symptoms, headache, muscle aches, nausea, pain, fever, diarrhea, infections.	[23, 62]

adverse effects if they enhance the interaction. Out of the eight tested secondary compounds curcumin was found to have strong interaction with protease of COVID- 19[19]. In another studies in silico screening with AI has been performed. It is a very fast method of screening reducing the cost of experiment as well as few human trials are required which leads to a fast development of drug[20].

Until now, many existing allopathic drugs are also being tried continuously which may prevent worsening of the clinical condition of the patient and provide them early relief. Some of them being given to the patients include remdesivir, lopinavir, chloroquine or hydroxychloroquine and interferon beta-1a. Recently, convalescent plasma therapy is being tried[21]. But all these medicines have many potentially serious side effects thus limiting their use to critical patients only. Moreover, the efficacy of these medicines has not yet been proven and thus are restricted to compassionate use only[22] (Table 4).

Randomised Control Trials are continuously being done to see and prove the efficacy of these drugs and to find an appropriate effective treatment. One of the biggest international clinical trials is being conducted by WHO which has been given the name “Solidarity”. Seeing the urgency of the need of an effective treatment against the COVID-19, this trial is said to reduce the normal time taken by 80%. Four regimens are currently included namely, remdesivir, lopinavir with ritonavir, chloroquine or hydroxychloroquine and lopinavir with ritonavir with interferon beta-1a[23].

Although same is the case with complementary medicine and their use is dependent upon their recorded effects in the treatment of SARS and MERS and upon the various small clinical trials and that their efficacy against COVID-19 is not yet proven, but the lack of potentially serious side effects gives us a possible and much needed window for their use in the treatment of COVID-19 not only in critical patients but also in patients with mild clinical disease. Although complementary medicine cannot replace modern medicine but can act as its supplementary. The integrated treatment can be clinically more effective and decrease the suffering of the patient in both time and severity. National Health Commission of the People's Republic of China, on Feb 17, reported that 60,107 confirmed COVID-19 patients were successfully treated with integration of Western medicine and Traditional Chinese Medicine[24,25]. Also, traditional pool can be exploited as a prophylactic medicinal source against the disease especially in high risk population by boosting up immunity, blocking the infection, cutting off the inflammatory storm and promoting repair of the body[24].

CONCLUSION

Although modern medicine came over traditional medicine in Darwinian process especially in developed countries, it is still being used widely by much of the population especially in developing countries. In fact, the trend is continuously growing towards the use of traditional medicine which is now no longer "the poor man's alternative to conventional care"[26]. Although the ancient traditional medicine seriously lacks validation and standardization[27], but the increasing tilt of the society towards the alternative medicine source due to widespread increasing rate of chronic diseases as well as lack of modern allopathic medicine in treating various infectious diseases due to antimicrobial resistance, has lead to various researches and studies which proves their efficacy and safety in various advanced clinical trials. Lately, when the world is under attack by COVID-19 and where modern medicine is incapable of saving us our heads turn towards the traditional medicinal source to be our shield. A lot of researches are being done to find the potential candidates from the conventional herbal pool which can prevent the spread and stop the effect of the virus.

In view of such newly emerging and re-emerging infectious diseases such as Ebola virus, Nipah virus, Zika virus, COVID-19, having potential to cause epidemics and thus seriously affect the human race not only in severity but also in numbers, traditional medicine can lend us a way out which, as quoted by WHO, is the care that is close to homes, generally available, accessible, affordable and sometimes the only care available to people at primary health care level[26].

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CONFLICT OF INTEREST

The authors declares that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ETHICS STATEMENT

Not applicable.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript and/or the Supplementary Files.

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