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MATHEMATICS OF COVID-19 IN INDIA AND THEIR POSSIBLE CONTROL BY *Allium sativum* (L.)

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Author HK designed the study and collected all the data on nCoronavirus and carried out garlic activity on viruses and managed the first draft and carried out corrections and got approved from author. Author VKS has draft the article and carried out corrections. Both authors read and approved the final manuscript.

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Review Article

ABSTRACT

SARS-CoV-2 belongs to the betacoronavirus genus. Betacoronaviruses infect mammals, are zoonotic pathogens, and can cause severe respiratory disease in human being. Till date there are no drugs or vaccine to control the infection of this pandemic disease. The present comprehensive review is therefore an effort to give detailed information about *Allium sativum* (Garlic) against nCoronavirus. The ayurveda and other traditional system of medicine in India described garlic and other medicinal herbs are used against various epidemics time-to-time. Alternatively, a number of literature noted that compounds extracted from garlic and other group of alliums such as allicin, diallytrisulfide, azoene and quercetin exhibit antiviral activity.

Keywords: Virus; COVID-19; *Allium sativum*; Ayurveda; garlic.

1. INTRODUCTION

The emergence of severe acute respiratory syndrome COVID-19 has offered the world a crash course in modern epidemiology, starting with lesions in case detection and exponential growth. The first human case of 2019-NCoV subsequently, named SARS-CoV-2 were first reported by officials in Wuhan city of Hubei province, China, in December, 2019 [1]. Retrospective investigation by Chinese authorities has identified human cases with onset of symptoms in early December, 2019. While some of the earliest known cases had a link to a wholesale food market in Wuhan city some did not, suggesting that the market in Wuhan city was the source of this outbreak or played role in the initial amplification of the outbreak [1].

Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease and cancer are more likely to develop serious illness. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes so it's important that you also practice respiratory etiquette [2].

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The World Health Organization, (WHO) [2] was declared a public health emergency of international concern on January 30, 2020 and on March 11, 2020 has declared the novel coronavirus (COVID-19) outbreak a global pandemic [2]. Till that the number of cases outside China increased 13 fold and the number of countries with cases increased three fold. The first case of the COVID-19 in India was reported on January 30, 2020. As of June 10, the Ministry of Health and Family welfare have confirmed a total of 276,583 positive cases (active cases 133,632 at 48.32 %), 135,206 recoveries at 48.88 % rate and 7,745 deaths at 2.80 % rate in the country. The infection rate in India is significantly lower than in the other affected countries. More than twenty-four thousands papers have been published worldwide in journals in very short span of time.

The early spread of COVID-19 has divulged critical information about potential size of the pandemic, if it were allowed to grow unchecked. This information can be mathematically studied with the help of mathematical modeling of infectious diseases. The total number of people infected in a population is determined by the intrinsic reproductive number, R_0. This number is the expected number of secondary cases caused by an index case in another susceptible population. Also, R_0 can be expressed as the transmission rate/ divided by the rate at which people recover or mortal. For accuracy describe R_0 in reference to a pathogen and host population, because the number is partially under host control. It also helps in determining the average long-term generality in the population, assuming new susceptible persons prevent the disease from dying out. As epidemic increases and few of the population become immune, the average number of secondary cases caused by an infected person is called the effective reproductive number R_t. In India a decline trend in COVID-19 cases or a small spring to summer epidemic might be taken as evidence that interventions have been especially effective or that herd immunity has been achieved [3] (Fig. 2).

As epidemic dies out when an average infection can no longer reproduce it. This occurs when large fraction of an infected hosts contacts is immune this threshold between where an infection can and cannot reproduce itself defines the fraction of the population required for herd immunity. It can be calculated precisely if the epidemiology of the pathogen is well known and is used to guide vaccination strategies. Herd immunity is constantly eroded by the births of new susceptible hosts and sometimes by the waning of immunity in previously infected host [1]. The durability of immunity to COVID-19 is not yet known till date, but births will promote virus survival. Thus like other transmissible pathogens, COVID-19 is likely to circulate in humans for many years to come. Steps taken by Indian Government are appreciable against pandemic COVID-19. The infection rate in India remains low relative with respect to large population size. Credit goes to fast action like Lockdown, physical distancing and susceptible people will be quarantine [1].

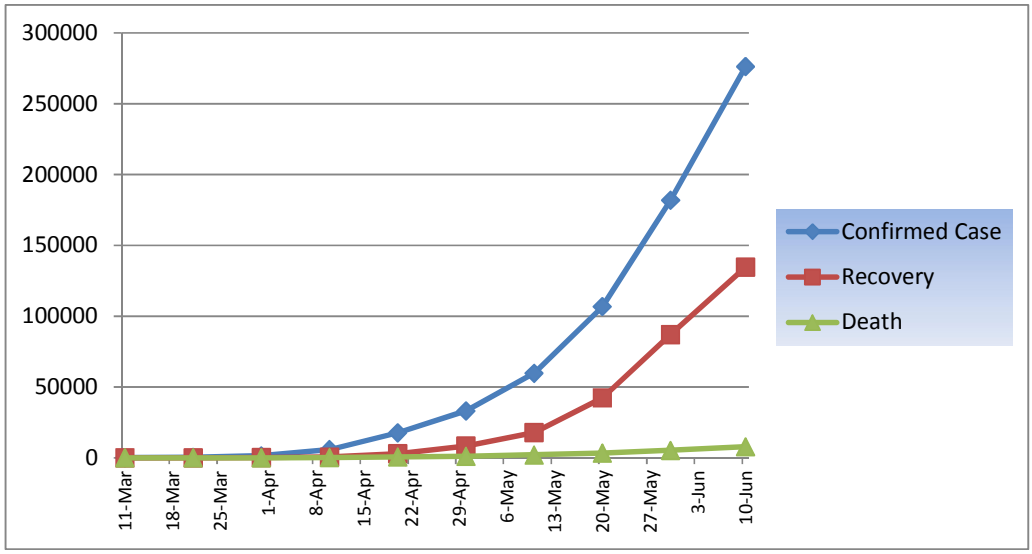

Fig. 1. Pandemic 2020 of COVID-19 infection, recovery and death rate in India

COVID-19 belongs to the Category- Coronaviruses; Order- Nidovirales; Family-Coronaviridae; Genus-Betacoronavirus; Species- SARS-CoV2. Betacoronaviruses can infect mammals, are zoonotic pathogens, and can cause severe respiratory disease in humans. Other viruses in this family are SARS coronavirus and MERS coronavirus. COVID-19 (SARS-CoV-2) has approximately 79% sequence identity to SARS-CoV and 50% to MERS-CoV [4]. Fehr et al. [5] published a research paper on Coronaviruses: an overview of their replication and pathogenesis in Methods Mol Biol. They report that COVID-19 (SARS-CoV-2) virus consists: a spike (S) protein, dimer (HE) hemagglutinin-esterase, a membrane (M) glycoprotein, an envelope (E) protein, a nucleocapsid (N) protein and ssRNA- Single standard ribonucleic acid (Fig. 3).

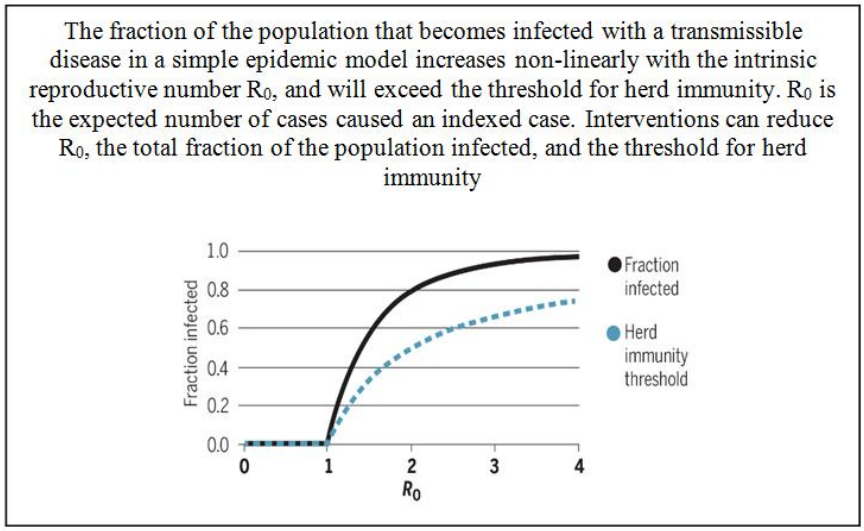

Fig. 2. Pandemic size and herd immunity
Source: Cobey S. Modeling infectious disease dynamics. Science 24 April 2020, 10.1125/science.abb5659

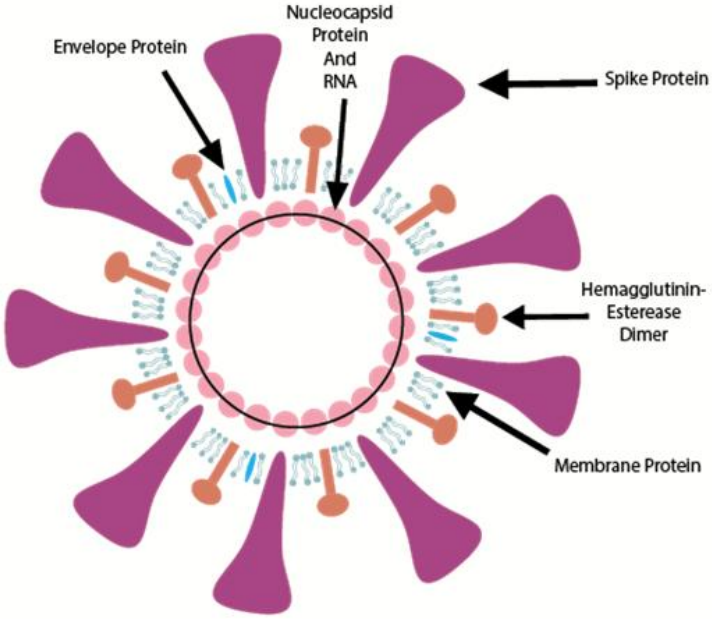

Fig. 3. COVID-19

Spike protein (S) - The surface of the spikes is homotrimers are mainly glycosylated. Trans membrane protease serin type 2 (TMPRSS2) [6] composed of two separate polypeptides S1 and S2, respectively. The subunit S1 form head of the spike has a receptor binding domain which ultimately binds to nCoronavirus host receptor ACE2. Subunit S1 triggers a conformational change in (S) protein and promotes membrane fusion with the help of Subunit S2.

ssRNA are largest of all RNA virus genome (single standard RNA genome) about ~27-32 Kb in size.

Nucleocapsid protein (N protein) is abundant phosphoprotein. N proteins contribute only protein with N-terminal and C-terminal. It binds the ssRNA genome in beads on a string type conformation.

Envelope protein (E) is the smallest (max. 109 amino acid) structural protein. It involves in various ways such as assembly, budding and formation of envelop etc. Envelop proteins E may oligomerize and form ion channel. This virion goes for pathogenesis.

Membrane protein (M) is the most abundant transmembrane (III) glycoprotein. It contains approximately 230 amino acids. It does not contain signal sequence and exists as a dimer in the virion. Glycoprotein M maintains the bioactive and antigenic character. It may have two conformations (long & compact) to onset and promote membrane curvature to bind with nucleocapsid.

Hemagglutinin-esterase dimer protein (HE) is present in N-coronaviruses. The HE protein attached with sialic acids receptor present on surface host cell surface. The protein activities are enhanced through S protein-mediated cell entry and virus spread by mucosa of the host [4].

2. GARLIC AND OTHER ALLIUMS ACT AS ANTIVIRUS

The Indian traditional system of medicine has both preventive and curative aspects. The preventive depends upon individually whereas curative involves the use of herbs as medicine. In Indian Medical history Charaka-Samhita and Sushrut-Samhita accredited to Charak a physician and Sushrut a surgeon. The Indian medicine were based on human body analysis in terms of earth, water, fire, air and ether as well as the three body humours- vata, pitta and kapha, respectively. In ancient Indian medicine garlic was a valuable curative condiment. Garlic, *Allium sativum* L. (Family: Alliaceae) has been widely recognized as a valuable spice and a general restorative for various ailments and physiological disorders. The name garlic may have originated from the Celtic word 'all' meaning pungent. Among oldest cultivated plants, garlic is mentioned in the Bible and in the literature of Ancient Israel (The Talmud), Egypt (Codex Ebers) and India (Vedas and Purans, Charak Sanghita) [7]. Garlic has been used as a restorative and first preventive medicine during various epidemics emerged time-to-time such as dysentery, cholera, influenza and typhus [8]. Researchers from various disciplines are now directing their efforts in connection with the effects of garlic on human health.

Interest in garlic among researchers, particularly those in medical profession, has stemmed from the search for a drug that has a broad-spectrum therapeutic effect with minimal side effect. A number of research studies indicate that garlic has antimicrobial activity against a number of bacteria (*Sacillus anthracis*), viruses (Rhinovirus type2) and fungi (*Cryptoccocal meningitis*). In 1720 garlic saved thousands residents of Marseille from the epidemic of plague. A broad spectrum of garlic was found to reduce the number of cholera in 1913, typhoid fever and diphtheria in 1918, respectively. During 1918 phytotherapists used garlic with success rate against great pandemic of influenza (Spanish fever) [8]. Low concentration of certain ingredients of garlic such as allicin, azoene, allyl methylthiosulphonate has strong antiviral activities against herpes simplex virus type1 and 2, parainfluenza virus type3 and vaccinia viruses. Mehrbod et al. [9] proved that garlic clove extract (CC_{50}-100 µl/Ml and EC_{50}-10) inhibits viral infection of influenza A (H_1N_1) and B. Similarly, garlic is effective against HIV, rhinovirus, herpes simplex virus 1 and 2, pneumonia and rotavirus [10,11].

Intact garlic clove consist medicinally active compounds [12,13]. Cutting, crushing or chewing of garlic cloves release the enzyme alliinase that rapidly lyses the cytosolic cysteine sulfoxide [14,15] to form sulfenic acid (R-SOH) [12], which immediately condenses to form allicin. It consists minerals (Mg, Zn, Se, Germanium), Vitamins (C and A) and enzymes etc. Garlic contains about 100 sulfur-containing compounds for medicinal purposes [13,16, 17,7]. Garlic is one of the most investigated medicinal plants by the researches worldwide. During 1960 to 2020, more than 5000 research articles have been published in the field of chemistry and biological effects of garlic and their preparations.

3. MECHANISM OF ACTION AGAINST VIRUS

Garlic and onions consist mainly organosulfur compound as allicin, diallytrisulfide and azoene and

flavonoids such as anthocyanins and quercetins [7, 18]. Garlic clove extract and their ingredient at low concentration as 0.1 ml has a strong inhibitory effect on nCoronavirus multiplication *in vivo* [19]. Chemicals present in onion and garlic block the formation of protein and genetic material in the viruses [20,21]. Elena and Sanjuan [22] noted that the high mutation rate of viral RNA polymerase enhances the development of this resistance in virus with RNA genome. Most of the antiviral drugs are ineffective against virus. So, virus develops resistance against these drugs. Alternatively, a natural drug from plant may inhibit the viral infection.

Antiviral drugs generally targeted the virus cycle like attachment, un-coating, replication of genetic material, translation and multiplication in the cell [23]. Flavonoids present in garlic may prevent the virus entry or inhibit for virus multiplication. Several studies confirm that flavonoid (quercetin) act against the virus in host. Takimoto et al. [24] noted that hemagglutinin and neuraminidase are envelope glycoprotein responsible for entry of virus (Influenza) into host cell. This glycoprotein helps in attachment and membrane fusion and facilitates the release of ribonucleic proteins into cytosol [24]. Then ribonucleic protein transported into the nucleus for its replication. Recently, Wu [25] reported the quercetin interact with virus haemagglutinin protein and check the virus entry into host cell. Further, Yao et al. [26] observed quercetin minimize virus infection by blocking viral attachment stage during infection. Several studies have provided that flavonoid (quercetin) can affect the viral multiplication by several ways. Chen et al. [27] noted that SARS-CoV protease was inhibited by quercetin during multiplication of the SARS virus in the host cell. Later Gonzalez et al. [28] reported quercetin inhibit the translation process of virus hepatitis C. Flavonoid also hit the cytokines in host cell. Cytokines are groups of proteins secreted by cells of immune system as macrophages, B and T lymphocytes and endothelial cells. Such cytokines are chemical messengers in cell signaling pathways. Garlic extract and their active compounds give anti-fibrotic effect as specific tissue transglutaminase inhibitors [29].

On the basis of published literature many scientists reported that the quercetin may increase phosphorylation of eukaryotic initiation factor (eIF2α) in response to virus infection finally checks the viral multiplication in the cell. Ganesan et al. [30] observed quercetin reduce the cleavage of elFG4II (eukaryotic initiation factor) and reduce the formation of viral capsid protein, it may affect the replication of Rhinovirus replication. Allicin and quercetin present in garlic plays important role in preventing the virus infection. Further more research needed to elucidate the mechanism of active component of garlic against the viral life cycle on most recent pandemic COVID-19.

4. CONCLUSIONS

It is fact that garlic is a nature's boon to humankind. Garlic contains sulphur compound and flavonoid for curing a human being by inhibiting the harmful viruses. Instead of several clinical tests, garlic is not yet widely recognized by medical authorities. More research should be undertaken in future to determine its efficacy as an anti-viral agent with respect to other natural product on one hand and modern drugs on the other. Therefore, garlic and other alliums require more attention by public health specialists and scientists to elucidate mechanism of action against virus COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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