

COVID-19 and the Use of Natural Products

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Coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by a new variant of coronavirus which has already spread in more than 150 countries and gained global attention. The absence of efficient and effective medicines towards this disease has indeed aggravated the situation [1]. Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) was an extremely contagious virus that caused serious disease and death. This virus has been found to cause human respiratory, enteric, and neurological disorders. This is one of the seven known coronavirus strains, found to inflict human infection and the latest outbreak of coronavirus in 2019 was triggered by the strain called SARS-CoV-2. Other strains include HCoV-NL-63, HCoV-229E, HCoV-OC43, HCoV-HKu1, MERS-CoV, etc. [2,3]. Coronavirus 2019 has quickly spread to the international community originating from Wuhan city, Hubei in China [4]. The exponential growth of this new coronavirus strain has already imposed strict four-tier guidelines in UK. In September 2019, it was first observed in UK. In mid-December, this amounted to almost two-thirds of population in UK [5]. On 30th January 2020, it was first reported in India through a student from Wuhan [13]. The world health organization (WHO) declared corona virus outbreak as a global pandemic on 11th March 2020 [12].

Considering the structure, there are four key proteins included in the structural composition of coronaviruses. Those are Spike (S),

Membrane (M), Envelope (E) and Nucleocapsid (N). Spike, a trimeric glycoprotein of CoV, establishes CoV variability and host tropism and also facilitates CoVs which bind to virus-cell membrane fusion and surface-specific receptor [6]. SARS-CoV-2 enters cells through this structural spike protein (S), which bind to the angiotensin converting enzyme-2 (ACE-2) receptor. Host cell receptors and endosomes are used by the spike proteins (S) to enter the cells after receptor binding. The transmembrane protease serine 2 (TMPRSS2), a host type 2 transmembrane serine protease, enables cell entry through the S-protein. The viral polyproteins which code for replicase transcriptase complex are synthesized once within the cell. SARS-CoV-2 synthesizes RNA through RNA dependent RNA polymerase enzyme. Structural proteins are generated, resulting in the formation and discharge of viral particles. The forthcoming drug treatments are included in these stages of the viral life cycle. Non-structural proteins like RNA dependent RNA polymerase, papain proteases, 3-chymotrypsin-like proteases which establish homologies with the other novel coronaviruses, are considered as promising medication targets. Additional drug targets include entry of virus and immune control [7]. At the time of sneezing and coughing, infection can transmit by enormous droplets through the symptomatic individuals. The infection may also occur in asymptomatic people before the symptoms start. In comparison to throat, studies indicate higher nasal cavity viral loads, with no viral load

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difference between asymptomatic and symptomatic individuals. The infection comes from the inhalation or contact with surfaces infected with such droplets, accompanied by the touch of the nose, eyes and mouth [4].

Natural products have been found to play significant role throughout the decades in prevention and treatment of several diseases. The essential oils and extracts derived from plants and animals are regarded as commendable source of biologically active molecules. A variety of natural products have already been reported as antiviral against enterovirus, hepatitis B, dengue, Influenza virus, coronavirus, and human immunodeficiency virus [8].

A research done by Wen et al. in 2007 examined that twenty-two terpenoids and lignoids could suppress SARS-CoV replication in African Green Monkey Kidney (Vero) E6 cells. The cytotoxicity of the metabolites against Vero E6 cells has been assessed and the inhibitory activity has been examined. The most active secondary metabolites have been reported as betulonic acid, savinin, ferruginol, 3 β ,12-diacetoxyabieta-6, 8-11,13-tetraene and 7 β -hydroxydeoxycryptojaponol, respectively. These compounds were known as powerful effective inhibitors of viral replication at concentrations of 0.63, 1.13, 1.47, 1.39, 1.57 and 1.15 μ M respectively [2]. Emodin, an anthraquinone from *Rheum officinale* Baill, and *Reynoutria multiflora* (Thunb.) Moldenkehas been used as anti-bacterial and anti-inflammatory agent. Ho et al. confirmed in 2007 that emodin inhibited the binding of S protein to ACE-2 and reduced infection of pseudo-typed S protein in cells of Vero E6. The dose-dependent interaction between S and ACE-2 was completely prevented by emodin with an IC₅₀ of 200 μ M, suggesting that it can be a therapeutic agent for SARS treatment [9]. Some of the popular natural immune boosters such as herbal medicines are useful in COVID-19 prevention. Herbal medicines include *Glycyrrhiza glabra*, *Zingiber officinale*, *Echinacea* spp., *Nigella sativa*, *Hypericum perforatum*, *Allium sativum*, *Camellia sinensis*. In addition, natural products play a significant role in the prevention of infection, especially in high-risk patients suffering from coronavirus infections [10].

Luo et al. stated that *Atractylodis macrocephalae*, *Glycyrrhizae uralensis*, *Lonicerae japonica*, *Astragalus mongholicus*, *Saposhnikovia*

divaricata, *Atractylodes lancea*, *Forsythia suspensa*, *Cyrtomium fortunei*, *Agastache rugosa* were used in the prophylaxis of COVID-19 [11]. Inhibitory activity against SARS-CoV papain-like protease (PL^{pro}) and SARS-CoV 3-chymotrypsin-like proteases (3CL^{pro}) with IC₅₀ values of 1.2 and 11.4 μ M, respectively is reported from a chalcone named xanthoangelol E, which is isolated from the ethanolic leaf extract of *Angelica keiskei* [2].

The outbreak of this new strain of coronavirus has challenged medical, economic, and public health infrastructure of many countries. The outbreaks of these kinds of viruses and pathogens are very much probable to continue in future. Natural products have a pivotal role in the prophylaxis or prevention of COVID-19. But there is no such evidence in the literature that it can also prevent the mutant strain of coronavirus. Therefore, efforts should be implemented to devise measures and investigate the utilization of natural products more precisely which can prevent such outbreaks of viruses in the future.

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Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV: severe acute respiratory syndrome-Coronavirus; WHO: world health organization; ACE-2: angiotensin converting enzyme-2; TMPRSS2: transmembrane protease serine 2