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INSIGHTS INTO USING PLANTS IN MANAGEMENT OF VIRAL DISEASES.

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At the end of 2019, the world encountered a devastating disease caused by a corona virus SARS-CoV-2 and named after it COVID-19. Its high morbidity and mortality resulted in a worldwide healthcare emergency, which in turn accelerated and amplified efforts in the relevant areas of health sciences research and practice.

The entire genome of SARS-CoV-2 was sequenced and made public on GISAID (accession ID: EPI_ISL_402119; EPI_ISL_402120; EPI_ISL_402121)[1]. When compared to the genomes of other viruses, the SARS-CoV-2 genome has 79.5% nucleotide similarity with SARS-CoV, which appeared in Guangdong Province in China in 2002, about 50% similarity with MERS-CoV, which emerged in the Middle Eastern countries in 2012, and 96% similarity with the bat coronavirus CoV RaTG13[1].

Reaching herd immunity by achieving a 70-80% vaccination rate became a primary strategy to tackle the pandemia. Just in about a year from virus identification, on December 11, 2020, Pfizer-BioNTech COVID-19 Vaccine became available in the USA under the Food and Drug Administration (FDA) Emergency Use Authorization. Since then multiple COVID-19 vaccines have mushroomed around the world including Oxford–AstraZeneca (Vaxzevria, Covishield), Pfizer–BioNTech (Comirnaty), Moderna (Spikevax), Janssen (Johnson & Johnson COVID-19 vaccine), Sinopharm (BBIBP-CorV), Gamaleya Research Institute of Epidemiology and Microbiology (Sputnik V), Bharat Biotech International Limited (Covaxin) and more than 20 others in various stages of development and approval. However, management of COVID-19 disease remains complex, and thus it is a rapidly developing field of research and clinical implementation.

The human body hosts an innumerable variety of viruses, described as the 'virome'. It is estimated at approximately 10^{13} particles per individual, with great heterogeneity[2]. A recent evolutionary analyses of human genomic datasets unveiled that a strong genetic adaptation going 25,000 years back exists in East Asian human populations, where multiple genes interact with coronaviruses, including SARS-CoV-2 that started 25,000 years ago[3].

Medicinal plants have been used for the treatment and mitigation of viral diseases long before 1796, when Edward Jenner demonstrated that the "vaccinia" virus could protect against smallpox, and even before variolation was used in China and India more than two millennia ago. For hundreds of years, the Native Americans who were severely affected by smallpox, used poultices and infusions derived from *Sarracenia purpurea* to treat the disease. The antiviral properties of this plant were confirmed in the modern experiments[4].

During the desperate times of the Spanish Flu pandemic, people used herbal remedies such as *Allium cepa*, *Gelsemium sempervirens*, *Eupatorium perfoliatum*, *Actaea racemosa* and *Asclepias tuberosa* to alleviate disease burden. Oseltamivir (Tamiflu®), a drug derived from *Illicium verum* is FDA approved for the treatment of acute, uncomplicated influenza in patients two weeks of age and older who have been symptomatic for no more than 2 days. It is also available for prophylaxis of influenza in patients 1 year and older[5].

The key steps in virus replication cycle are well researched[6]. The findings prompted the identification of targets for the novel compunds and fine-tuning of the existing botanical entities. Those targets may include the phases of SARS-CoV-2 entry, RNA replication, synthesis of polymerases, proteases, nonstructural and structural proteins, as well as adaptive immune responses to SARS-CoV-2 infection. Plants contain millions of natural compounds, however traditional screening for the compounds effective against SARS-CoV-2 is a very lengthy and labor-consuming process. A recently developed computational prediction process can be utilized as a rapid and efficient technique that

engages the interaction between the plant in question and the spike (S) and the nucleocapsid (N) proteins of SARS-CoV-2.

Obstructing the attachment of S protein to angiotensin converting enzyme 2 (ACE2) receptors is an attractive and promising therapeutic modality in the management of COVID-19. The feasibility of such a blockade can be accomplished by a number of compounds derived from the plants; as for example, it was shown for licoflavonol from *Glycyrrhiza uralensis*, emodin from the genus *Rheum* and *Polygonum*, baicalin from *Scutellariabaicalensis*, scutellarin from *Erigeron breviscapus*, 1,3,4,6-tetra-O-galloyl-β-D-glucose from *Galla chinensis*, luteolin from *Veronicalinariifolia.*

Coronaviral non structural proteins, such as RNA-dependent RNA Polymerase (RdRp), is a critical enzyme involved in the virus's RNA replication, transcription and protein translation, as well as in the modification and processing of proteins. RdRp has been used as an important target to develop drugs against SARS, MERS and SAR CoV-2. Some medicinal plants have demonstrated pharmacological activity by binding to RdRp. Another enzyme responsible RNA replication and maturation of the viral polyproteins is 3-chymotrypsin like protease (3CLPro). Betulonal (*Cassinexylocarpa*), gnidicin and gniditrin (*Gnidialamprantha*) bind to and inhibit the RdRpof coronaviruses. Betulonal has been shown to inhibit both the RdRp and 3CLPro.

Neuraminidase is an essential enzyme required for viral spread across the host cells. Oseltamivir, as a neuraminidase inhibitor blocks the release of viruses from the infected cells, thus shortening the disease duration.

Anti-inflammatory and immunomodulatory compounds work by inhibiting the pathological inflammatory response induced by SARS-CoV-2 and other viruses. Their effects impede the pathogenesis by decreasing cytokine production, specifically the release of IL6, IL1β and TNFα, and hindering cellular autophagy in the infected cells. Blocking the interleukin signaling pathway may control the release of cytokines caused by SARS-CoV-2 infection. Many flavonoids inhibit inflammatory cytokines thus exerting immunomodulatory and anti-inflammatory effects. For example, liquiritin, a flavonoid extracted from the roots of *Glycyrrhiza uralensis* acts similarly to interferons hence eliciting such a response.

Botanical therapeutics possess a unique potential in the treatment of viral diseases. The pharmacological base and clinical use of botanical therapeutics have been extensively reviewed[7-8]. The mode of action(s) may be built either on the direct interference with the virus ability to enter human cells, virus replication, or exerting immune-modulatory and anti-inflammatory effects. The adjuvant treatment with botanical therapeutics has the potential to result in advances in symptom resolution, decrease in disease burden and shortening its duration.

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