International Journal of Phytopharmacology

Review Article

www.onlineijp.com

e- ISSN 0975 – 9328
Print ISSN 2229 – 7472

MEDICINAL PLANTS SCREENING IN THE MANAGEMENT OF COVID-19 BASIS ITS MODE OF ACTION – A REVIEW

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ABSTRACT

Flora of India is rich in a variety of species with various potential active ingredients that have been widely used to treat a variety of infectious and non-infectious diseases. A number of medicinal plants have shown promise to treat a number of viral infections, and some of them possess broad-spectrum antiviral activity. In the past, discovery into the antiviral activity of various medicinal plants was limited due to highly infectious nature of viruses and short of suitable separation methods for the screening of antiviral components from plants. In the pandemic spread of Covid-19, search and development of an ideal treatment is very essential and based on the observation with the world wide scenario a search was made to identify medicinal plants with antiviral activities possessing immuno-modulator, RNA viral inhibition, hepatitis viruses, chloroquine derivatives, ACE2 inhibitor etc. Further to enhance its efficacy search of nutritional supplements like Zinc and Vitamin C which are considered to be a main stay in developing a novel drug. An advancement of such approaches, in which non-infectious molecular clone of a virus could be used for antiviral screening purposes, and development in separation technologies offers promise for medicinal plants usage in modern drug discovery. This article describes potential antiviral properties of medicinal plants against a diverse group of viruses, and suggests screening the potential of plants possessing broad-spectrum antiviral effects against emerging Covid-19 infections.

Key words: Covid-19, viral infection, Antiviral drug, medicinal plants, immuno-modulator, ACE2 inhibitors.

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Covid-19 is a pandemic disease representing a serious health issues to human, worldwide, affecting most of the community. In the past twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and H1N1 influenza have been recorded. Recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was also identified in Saudi Arabia.

Access this article online		
DOI: **http://onlineijp.com/** DOI: **http://dx.doi.org/10.21276/ijp.2020.11.2.3**		**Quick Response code**
Received:25.04.20	**Revised**:12.05.20	**Accepted**:15.06.20

In the present day, an epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province and the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019".

This new virus seems to be very contagious and has quickly spread globally. Initially, the new virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoVs) (Marco Cascella *et al*., 2020). The CoVs have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species (Perlman and Netland, 2009). For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. SARS-CoV-2 are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV), and Gammacoronavirus ($_{\gamma}$CoV). Furthermore, the βCoV genus divides into five sub-genera or lineages (Chan *et al.*, 2013). Genomic characterization has shown that probably bats and rodents are the gene sources of αCoVs and βCoVs. On the contrary, avian species seem to represent the gene sources of δCoVs and $_{\gamma}$CoVs. Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. As on date, seven human CoVs (HCoVs) are being identified to be infecting humans. Interestingly, some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium. In general, estimates suggest that 2% of the populations are healthy carriers of CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections (Chen *et al.*, 2020).

Currently, the world is now desperate to find ways to slow the spread of the novel coronavirus “SARS-CoV-2”and to find effective treatments. At present there is no specific treatment recommended for SARS-CoV-2, and no vaccine is currently available. But on the treatment module recommended by regulatory bodies suggest the usage of Chloroquine, Antiviral drugs, Vitamin C, Zinc supplement, ACE2 inhibitors, RNA viral inhibitors, Plasma therapy, etc (Marco Cascella *et al.*, 2020). Based on this screening was carried out in medicinal plants to collect information and scientific evidence and to provide an overview of the topic which could be further subjected for detailed evaluation on the treatment for SARS-CoV-2.

Antiviral drugs from plant sources:

The molecular mechanisms associated with the antiviral effects of plant extracts may vary among different viruses. However, the potentials of plant extract to boost inherent antiviral defense of human body which involves an intricate immune system might utilize common pathways. In recent past, a number of studies have explored immunostimulatory properties of plant extracts having antiviral properties (Webster *et al.*, 2006).

Ethnopharmacology provides an alternative approach for the discovery of antiviral agents, namely the study of medicinal plants with a history of traditional use as a potential source of substances with significant pharmacological and biological activities. The Indian subcontinent is endowed with rich and diverse local health tradition, which is equally matched with rich and diverse plant genetic source. A detailed investigation and documentation of plants used in local health traditions and ethnopharmacological evaluation to verify their efficacy and safety can lead to the development of invaluable herbal drugs or isolation of compounds of therapeutic value. A number of compounds extracted from various species of higher plants have shown antiviral activity. Examples included tannins, flavones, alkaloids, that displayed *in vitro* activity against numerous viruses (Vijayan *et al*, 2004).

Medicinal Plants effective against Hepatitis viruses:

Screening of medicinal plants against Hepatitis Virus was done basis the activity of inhibition of RNA virus, with special reference to Covid-19, which is also an RNA virus. Hepatitis in general is an inflammatory disorder of the liver, caused by Viruses. The most common type of viral hepatitis are Hepatitis A, Hepatitis B and Hepatitis C, while all three type of hepatitis can cause similar symptoms each virus can spread in different ways. Medicines are limited due to poor long-term response, high rate of adverse side effects and the emergence of resistant mutants, which occur during the period of long-term therapy. Therefore, the discovery of safe and effective anti-HBV drugs is still considered a serious challenge. Herbal medicines have long been used for the treatment of liver disorders all over the world, and a number of them exhibit anti-HBV activity, which has been proved experimentally in preclinical and clinical studies. Meta-analysis in clinical trials showed that extracts from *Phyllanthus* species have a positive effect on the clearance of serum hepatitis B surface antigen (HBsAg) in HBV carriers (Liu *et al.*, 2001). For example, *P. amarus* has shown to exert its antiviral effect via interaction with HBV enhancer I and C/EBP alpha and beta transcription factors, thus inhibiting the HBV polymerase activity and mRNA transcription (Lee *et al.*, 1996; Ott *et al.*, 1997). In fact, various studies have reported that plants have antiviral properties against hepatitis virus. For example, *Oenanthe javanica* has been shown to be helpful in the treatment of HBV infection and to inhibit HBsAg and HBeAg secretion *in vitro* (Huang *et al.*, 2001). Jacob *et al.*, (2004) investigated that KYH-1 (an aqueous extract of herbal formulation) showed potent antiviral activity and suppressed HBV replication in a human hepatoblastoma cell line. Thus, the use of medicinal plants becomes an interesting target for research to substitute the conventional drugs and chemicals. More research is needed to focus on the screening of the antiviral activity of medicinal plants on HBV (Table 2).

There are few studies regarding the novel mode of action of natural products against HBV. For example, *Acanthus ilicifolius* L. reduces HBV-induced liver damage by lowering the transaminase (Wei *et al*., 2015). *Gymnema sylvestre* R.Br. shows antiviral activity and its phytoconstituents inhibit HBsAg binding and HBV DNA polymerase (Subashini *et al*., 2015). Also, the extract from *Phyllanthus* reduces HBV DNA synthesis and HBsAg and HBcAg secretion by replicating cells harbouring HBV wild-type and LMV-resistant mutants, may be by inducing the expression of interferon-beta, cyclooxygenase-2 and interleukin-6 via activation of extracellular signal-regulated kinases and c-jun *N*-terminal kinases (Jung *et al*., 2015). Curcumin inhibits HBV gene expression and DNA replication, mediated by down-regulation of PGC-1α, a starvation-induced protein that initiates the gluconeogenesis cascade and that may robustly co-activate HBV transcription (Rechtman *et al*., 2010). Overall, there are not sufficient studies on the mechanism of action of active constituents of plants against HBV, although many natural products have been found effective against HBV inhibition in many studies.

Chloroquine derivatives / Antimalarial drugs from plant sources:

Currently, Chloroquine and Hydroxychloroquine are advocated in the treatment of SARS-CoV-2 along with antibiotics. The probable mode is that it can block viruses, including SARS-CoV-2 - from getting inside cells and prevent infection along with zinc. Based on this medicinal plants advocated in the management of malaria were screened. Crude extracts of species of Simaroubaceae, namely *Brucea javanica* and *Simaba cedron*, both of which are used in traditional medicine for the treatment of malaria, and of *Ailanthus alitissima*, were prepared for evaluation by the *in vivo* test using sequential fractionation solvents like petroleum ether, methanol, and aqueous extracts; the methanol extracts were subsequently partitioned between chloroform and water. The three species yielded active extracts and in each case the activity was concentrated in the chloroform fraction. The ability of the *in vitro* test to detect active compounds in relatively crude fractions has been further demonstrated by assessing the activity of *B. javanica* fractions obtained from polyamide columns. Clearly, an *in vitro* test against multi-drug resistant *P. falciparum* that can be used for the evaluation of crude extracts of plants, has considerable value for the assessment of plants used in traditional medicine for the treatment of malaria (O'Neill *et al*., 1985).

The most significant recent development in naturally occurring antimalarial drugs is arguably the identification of artemisinin as the active component of the plant *Artemisia annua*, which is used in traditional medicine as an antimalarial agent. This unique sesquiterpene contains an endoperoxide group that appears to be an essential requirement for its activity. It is particularly active *in vivo* against chloroquine-resistant *P. falciparum* and is reported to have relatively low toxicity. However, in the usual dose of 0.6 mg/day for 3 days, the average recurrence rate is more than 10%. Due to its highly lipophilic nature, there are inherent problems with its administration as a drug and several derivatives have been prepared, including arthemeter (methyl dihydroartemisinin) and sodium artesunate (sodium dihyroartemisinin hemisuccinate). Artemisinin and its two derivatives have been used clinically for the treatment of cerebral malaria in an area where chloroquine resistance was endemic and the cure rate was greater than 90%. The mode of action is not primarily at the level of nucleic acid synthesis but it appears to inhibit protein synthesis (Li *et al*., 1982; Gu *et al*., 1983). Like most naturally-occurring therapeutic agents, artemisinin exists in the plant in very small concentration. Chinese workers were unable to find artemisinin in about 30 other *Artemisia* species. In another attempt, a group at the Walter Reed Army Institute of Research studied some 70 species and did not find artemisinin in any of them (Klayman, 1993). *Alstonia scholaris* bark methanol extract exhibited antiplasmodial activity against multidrug resistant K1 strain of *Plasmodium falciparum* cultured in human erythrocytes and pet ether extract was effective in mice against *P. berghei* (Kalaria *et al.,* 2012). Further Ursolic acid showed a synergistic effect with ampicillin and tetracycline against both *Bacillus cereus* and *S. aureus*, which is an added benefit of the plant (Chao-Min Wang *et al.,* 2016). *Glycyrrhiza glabra* was found to be effective against *Plasmodium falciparum* and *P. berghei* which demonstrated antiplasmodial activity (Esmaeili *et al*., 2009). *Artemisia diffusa* was effective on *P. berghei*, where it was decreasing parasitaemia and inhibits its growth (Rustaiyan *et al*., 2009). Medicinal Plants like *Artemisia khorasanica* was successfully tested against *P. berghei* (Nahrevanian *et al*., 2010). Similarly *Artemisia annua* and *A. absinthium* reduced parasitaemia against *P. bergei* in mice by 94.28% and 83.28% (Ramazani *et al*., 2010a). *Prosopis juliflora, Boerhavia elegans* and *Solanum surattense* were chloroquine-resistant and sensitive strains against *P. falciparum* was effects with IC_{50} of 50 µg/ml and also possessed a good antiplasmodial activity *P. berghei* (Ramazani *et al*., 2010b). Further the choloroquine derivatives which are being dealt can be evaluated on par with Remdesivir, Lopinavir/ritonavir like activity, which could enhance the understanding of any drug for development. Remdesivir is an intravenous antiviral drug that was developed to block infection with related coronaviruses and even Ebola, and is one of the drugs the WHO is helping to investigate. Remdisivir has already been shown to work against SARS-CoV-2 in cells in a dish in a lab as well as in mice infected with the virus. Remdesivir specifically targets key viral proteins involved in making new copies of the virus and prevents them from working. Whereas, Lopinavir & Ritonavir drug combination used against viruses like HIV. It works in a similar way to remdesivir by blocking key viral proteins called “proteases. Lopinavir/ritonavir has also been shown to be effective against SARS-CoV-2 in cell cultures as well as in mice and is being tested alongside an antiviral drug called interferon beta. This is currently used to treat Multiple sclerosis and can enhance the natural defense of the body cells against SARS-CoV-2.

Table - 1. Antiviral activity of medicinal plants

S.No.	Virus	Medicinal plants	Antiviral effect	Reference
1	Herpes simplex virus	*Carissa edulis* Vahl.	Exhibiting strong anti-HSV1, and 2 activities both *in vitro* and *in vivo*	Tolo *et al*., (2006)
		Phyllanthus urinaria L.	1346TOGDG and geraniin inhibited HSV1 and 2 respectively	Yang *et al*., (2007)
2	Influenza virus	*Geranium sanguineum* L.	Reducing the infectivity of various influenza virus strains *in vitro* and *in vivo*	Pantev *et al*., (2006) and Serkedjieva (1997)
		Sambucus nigra L.	Ederberry extract offers an efficient, safe and cost-effective treatment for influenza	Zakay-Rones *et al*., (2004)
3	Hepatitis B virus	*Boehmeria nivea* L.	Root extract reduced HBV production both *in vitro* and *in vivo*	Huang *et al*., (2006)
		Polygonum cuspidatum Sieb.& Zucc.	Inhibits hepatitis B virus in HBV cell line	Chang *et al*., (2005)
4	Hepatitis C virus	*Saxifraga melanocentra* Engl.& Irmsch.	1,2,3,4,6-penta-O-galloyl-beta-d-glucoside demonstrated antiviral activity	Zuo *et al*., (2005)
5	Poliovirus	*Guazuma ulmifolia* Lam.	Inhibited polioviral replication and blocked the synthesis of viral antigens in infected cell cultures	Felipe *et al*., (2006)
6	Viral haemorrhagic septicaemia virus	*Olea europaea* L.	Leaf extract inhibited viral replication	Micol *et al*., (2005)
7	Severe acute respiratory Syndrome – associated coronavirus (SARS-CoV)	*Lycoris radiate*	Lycorine, possesses anti-SARS-CoV	Li *et al*., (2005)
8	Human immunodeficiency virus	*Phyllanthus amarus* Schum.& Thonn.	Inhibits HIV replication both *in vitro* and *in vivo*	Notka *et al*., (2004)
		Olea europea L.	Inhibits IV -1 acute infection and cell-to-cell transmission	Lee-Huang *et al*., (2003)
9	Vesicular stomatitis virus	*Trichilia glabra* L	Leaves extract inhibits VSV	Cella *et al*., (2004)
10	Human adenovirus type 1	*Glycine max* (L.) Merr.	Inhibition of human Adenovirus type 1 & Coxsackievirus B1	Yamai *et al*., (2003)
11	Dengue virus type-2	*Azadirachta indica* Juss.	Inhibited DEN-2 both *in vitro* and *in vivo*	Parida *et al*., (2002)

DEN-2 - Dengue virus type-2 ; HBV – Hepatitis B Virus; HIV - Human Immuno Deficiency Virus, HSV- Herpes simplex virus ; SARS-CoV - Severe Acute Respiratory Syndrome- Corona virus; VSV - Vesicular stomatitis virus

Table 2. Plants having effect against Hepatitis virus A, B & C.

S.No.	Botanical name	Hepatitis Viruses *	References
1	*Acacia nilotica* (L.) Willd. ex Delile	HCV	Hussein *et al*., (2000)
2	*Boehmeria nivea* L.	HBV	Lee *et al*., (1996)
3	*Boswellia carterii* Birdw.	HCV	Hussein *et al*., (2000)
4	*Embelia schimperi* Vatke	HCV	Hussein *et al*., (2000)
5	*Mentha longifolia* (L.) Huds	HAV	Al-Ali *et al*., (2010)
6	*Ocimum basilicum* L.	HAV	Al-Ali *et al*., (2010)
7	*Phyllanthus amarus* Schum. & Thonn	HBV	Ott *et al*., (1997)
8	*Piper cubeba* Linn.	HCV	Hussein *et al*., (2000)
9	*Quercus infectoria* Olivier.	HCV	Hussein *et al*., (2000)
10	*Saxifraga melanocentra* Franchet.	HCV	Zuo *et al*., (2005)
11	*Silybum marianum* (L.) Gaernt	HCV	El-Adawi *et al*., (2011)
12	*Swertia chirayita* (Roxb. Ex. Fleming)	HBV	Zhou *et al*., (2015)
13	*Swertia patens* Burkill.	HBV	He *et al*., (2016)
14	*Syzygium aromaticum* (L.) Merr. & L.M.Perry.	HCV	Hussein *et al*., (2000)
15	*Trachyspermum ammi* L. Sprague	HCV	Hussein *et al*., (2000)
16	*Zingiber officinale* Rosc.	HCV	El-Adawi *et al*., (2011)

***HAV -** Hepatitis A virus**, HBV -** Hepatitis A virus**, HCV -** Hepatitis A virus

Immunomodulatory Plants:

A large population of India uses plants for its healing, preventive, curative and much therapeutic property together with immunomodulatory property (Archana *et al*., 2011). Certain medicinal plants promote positive health and maintain resistance against infection by re-establishing body equilibrium. Many polysaccharides isolated from higher plants are considered to be biological response modifier and enhance various immune responses, like complement activation, proliferation of lymphocytes and stimulation of macrophages. Plant flavonoids, also used as immunostimulator, is important for growth, development and immunity (Mahiunddin Shaikh, 2010). Various synthetic agents are used as immunostimulative agent such as levamisole, thalidomide, but there are various side effects of these agents such as nephrotoxicity, hepatotoxicity, bone marrow depression, gastrointestinal disturbance and so on. Because of the side effects associated with synthetic agents and as plants are safer, some of the Indian medicinal plants with immunomodulation property are given in Table - 3. Much more effective and cheaper, conventional immune-modulator plants can be explored (Kumar *et al*., 2011).

Plants with immono-modulatory properties:

Panax species:

Ginseng is the dried root of various species of panax like *Panax ginseng* (Korean), *Panax japonica* (Japanese), *Panax notoginseng* (Chinese) and *Panax quinquefolium* (American). It contains triterpene glycosides, or saponins, commonly referred to as ginsenosides. Many active compounds can be found in all parts of the plant, including amino acids, alkaloids, phenols, proteins, polypeptides, and vitamins B1 and B2. *Panax ginseng* is often referred to as an adaptogen, which suggests it has varied actions and effects on the body that support nonspecific resistance to biochemical and physical stressors, improve vitality and longevity, and enhance mental capacity. Reviews suggest *Panax ginseng* has immuno-modulating activity by affecting the hypothalamic - pituitary-adrenal (HPA) axis. *In vitro* experiments reveal enhanced natural killer (NK) cell activity and increased immune cell phagocytosis after ginsenoside exposure. According to a 1999 World Health Organization review, ginseng saponins are thought to decrease serum prolactin, thereby increasing libido in male impotence (Gopalkrishnan *et al*., 2002; Chadwick and Marsh, 1997; Fatma *et al*., 2005).

Table 3. Plants with immuno-modulator properties

S. No.	Botanical name	Parts used	Active compounds	Mode of action *	Reference
1	*Acacia catechu* (L.f.) Willd.	Bark	Cyanidanol	Cell mediated & Humoral Immunity	Namrata Singh *et. al.*, (2012)
2	*Aesculus indica* (Wall. ex Cambess.) Hook.	Leaf	Flavonoids, Tannin	Cell mediated immune response	Manda Ram Mohan *et. al.*, (2019)
3	*Allium sativum* L.	Aerial parts	Organosulfur compound	IL	Archana *et. al.*, (2011)
4	*Aloe vera* (L.) Burm. F.	Leaves	Phenolic compounds	Cellular Immune response	Singh Virendra Kumar *et. al.*, (2011)
5	*Andographis paniculata* (Burm. f) Wall. ex Nees	Whole plant	Andrographolide	Pagocytosis	Namrata Singh *et. al.*, (2012)
6	*Asparagus racemosus* Willd.	Root	Steroidal saponins, Shatavaroside A, Shatavaroside B	Cell mediated immune response	Manda Ram Mohan *et. al.*, (2019)
7	*Azadirachta indica* Juss	Leaf	Limonoids	Humoral & cell mediated immune response	Alzohairy, (2016)
8	*Baliospermum montanum* (Willd.) Mul. Arg	Root	1-(3′,4′-dimethoxyphenyl) propan-1-one or propioveratrone, 1-(3′,4′,5′-trimethoxyphenyl) propan-1-one; 1-(2′-hydroxy- 4′, 5′-dimethoxyphenyl) propan-1-one.	Cell mediated immune response	Kalpana Patil *et. al.*, (2009)
9	*Balanite roxburghi* Planch	Leaves	Phenolic, Flavonoid compounds	IL	Archana *et. al.*, (2011)
10	*Bauhinia vareigata* Linn.	Stem bark	Lupeol, kaempferol, flavonone, Quercetin	Humoral antibody response	Ghaisas *et. al*., (2009).
11	*Boerhaavia diffusa* L.	Whole plant	Punarnavine	TNF-α, IL-1β, IL-6	Namrata Singh *et. al.*, (2012)
12	*Caesalpinia bonducella* L.	Seed	Saponins, Terpenoids	Phagocytosis	Singh Virendra Kumar *et. al.*, (2011)
13	*Capparis zeylanica* L.	Leaf	Glucoiberin, Glucocapparin, Sinigrin, Glucocleomin, Glucocapangulin, Glucobrassicin, Neoglucobrassicin	Humoral Immune response & Phagocytosis	Manda Ram Mohan *et. al.*, (2019)
14	*Centella asiatica* L.	Whole plant	Triterpenes	Cell mediated & Humoral Immune response	Manda Ram Mohan *et. al.*, (2019).
15	*Chlorophytum borivilianum* Santapau & R.R.Fern.	Roots	Saponins, Alkaloids	TH-1 type immune response	Rupinder Kaur and Sukhbir Kaur, (2020)

16	*Cissampelos pareira* L.	Roots	Alkaloids	Humoral	Singh Virendra Kumar *et. al.*, (2011)
17	*Cleome gynandra* L.	Aerial parts	Flavonoids	Suppresses humoral antibody response	Kori *et. al.*, (2009)
18	*Couroupita guinensis* Aubl.	Flowers	Ketosteroids, Terpenoids, Alkaloids,	Cell mediated immune response	Sumathi and Anuradha, (2017)
19	*Curculigo orchioides* Gaertn	Root	Curculigoside	Humoral Immune response	Rathod *et. al.*, (2010)
20	*Curcuma longa* L.	Rhizome	Curcuminoids	IL-2, Cytokines	Singh Virendra Kumar *et. al.*, (2011)
21	*Cynodon dactylon* Pers.	Whole plant	Tetramethyl-2-hexadecen-1-ol, Hexadecanoic acid ethyl ester, Hydroquinone	Cell mediated immunity	Namrata Singh *et. al.*, (2012)
22	*Dioscorea japonica* Thunb.	Tubers	Diosgenin	Humoral Immunity	Namrata Singh *et. al.*, (2012)
23	*Eclipta alba* L.	Whole plant	Ecliptine, Verazine	Pagocytosis	Manda Ram Mohan *et. al.*, (2019).
24	*Epilobium angustifolium* L.	Whole plant	Oenothein B	NF-kappa B activation	Namrata Singh *et. al.*, (2012)
25	*Ficus carica* L.	Leaves	Ficin	Humoral antibody response	Anonymous, 2019
26	*Gymnema sylvestre* R. Br.	Leaves	Gymnemic acid	IFN-γ, IL-4, IL-2	Farzana Khan *et. al.*, (2019)
27	*Heracleum persicum* Desf. ex Fisch.	Fruits	Furanocoumarins, Flavonoids	Cellular & Humoral Immune response	Sharififar *et. al.*, (2009)
28	*Hibiscus rosasinensis* L.	Flowers	Flavonoids, Quercetin	Enhances IL-1α & decrease IL-2	Mishra *et. al.*, (2012)
29	*Mangifera indica* L.	stem bark	Mangiferin	Humoral antibody	Namrata Singh *et. al.*, (2012)
30	*Morinda citrifolia* L.	Fruit	Tectoquinone, Asperulosidic acid,	Humoral & cell mediated immune response	Madhukar Lohani *et. al.*, (2019)
31	*Morus alba* L.	Leaf	Anthocyanin, Flavanoids	Cell & Humoral Immune response	Namrata Singh *et. al.*, (2012)
32	*Nelumbo nucifera* Gaertn.	Seed	S-armepavine	Humoral antibody	Singh Virendra Kumar *et. al.*, (2011)
33	*Nyctanthes arbor-tristis* L.	Leaves	Arborside C, monogentiobioside ester of Crocetin	Humoral antibody response	Jain and Pandey, (2016)
34	*Ocimum sanctum* Linn.	Whole plant	Phenolic compounds	Cellular mediated immunity	Venkatachalam, V. V. and Rajinikanth, B. (2012)
35	*Picrorhiza scrophulariiflora* Pennell.	Whole plant	Iridoid glycosides	IFN-γ, IL-2, IL-4, IL-12	Namrata Singh *et. al.*, (2012)
36	*Piper longum* L.	Fruit	Piperine	Pagocytosis	Manda Ram Mohan *et. al.*, (2019)
37	*Prunella vulgaris* L.	Fruit-spikes	Prunellin	Inhibition of HIV-1 reverse transcriptase	Singh Virendra Kumar *et. al.*, (2011)

38	*Randia dumetorum* (Retz.) Poir	Fruit	Triterpenes, Saponins	Cell mediated Immunity	Satpute *et. al.*, (2009)
38	*Rhaphidophora korthalsii* Schott	Leaf	5,6-dihydroxyindole	IL-1, IL-12, IFN-γ	Singh Virendra Kumar *et. al.*, (2011)
40	*Rhododendron spiciferum* Franch.	Aerial Parts	Epicatechin	Cellular proliferation	Singh Virendra Kumar *et. al.*, (2011)
41	*Sophora subprosrate* L.	Aerial parts	Sophora subprosrate polysaccharide	Pagocytosis, IL-6, TNF-α	Namrata Singh *et. al.*, (2012)
42	*Terminalia chebula* Retz.	Aerial parts	Epigallocatechin gallate	IL	Archana *et. al.*, (2011)
43	*Tinospora cordifolia* (Thunb.) Miers.	Bark	Arabinogalactan polysaccharide, N-methyl-2-pyrrolidone,Nformyl annonain,11hydroxy mustakone, cordifoliosideA,tinocordiside,syringin,and magnoflorine	Lymphoproliferation	Namrata Singh *et. al.*, (2012)
44	*Trapa bispinosa* Roxb.	Fruits	Flavonoids	Cellular & Humoral Immune response	Samir Patel *et. al.*, (2010)
45	*Terminalia arjuna* (Roxb. ex DC.) Wight & Arn.	Bark	Polyphenols, Falvonoids	Humoral antibody	Namrata Singh *et. al.*, (2012)
46	*Withania somnifera* (L.) Dunal	Root	Glycowithanolides, Sitoindosides IX, X	Pagocytosis, IL-1, TNF-α	Namrata Singh *et. al.*, (2012)

*IL – Interleukin, IFN-γ - Interferon gamma, TNF - Tumor Necrosis Factor, TH-1 - T helper type 1

***Glycyrrhiza glabra* L.**

A number of components have been isolated from licorice, including a water-soluble, biologically active complex that accounts for 40-50 percent of total dry material weight. This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances. Glycyrrhizin, accounts for the sweet taste of licorice root. The beneficial effects of licorice can be attributed to a number of mechanisms. Glycyrrhizin and glycyrrhizic acid have been shown to inhibit growth and cytopathology of numerous RNA and DNA viruses, including hepatitis A9 and C, herpes zoster, HIV, Herpes simplex. Glycyrrhizin and its metabolites inhibit hepatic metabolism of aldosterone and suppress 5-ßreductase, properties responsible for the well-documented pseudoaldosterone syndrome. The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and glucocorticoid activity of glycyrrhizic acid. Licorice constituents also exhibit steroidlike anti-inflammatory activity, similar to the action of hydrocortisone (Anonymous, 1997; Wagner Hand Proksch, 1997; Mills, 1991; Ramsey and Chlling, 1997).

Zingiber officinale **Rosc.**

The rhizomes of Ginger contain a number of pungent constituents and steam distillation of powdered ginger produces ginger oil, which contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene. The major pungent compounds in ginger, from studies of the lipophilic rhizome extracts, have yielded potentially active gingerols, which can be converted to shogaols, zingerone, and paradol. The compound 6-gingerol appears to be responsible for its characteristic taste. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products. The mechanism underlying ginger’s anti-emetic activity is not clearly understood, but the aromatic, spasmolytic, carminative, and absorbent properties of ginger suggest it has direct effects on the gastrointestinal tract. A mechanism involving the central nervous system cannot be ruled out, considering several of gingers components antagonize serotonin type-3 receptors; however, this has not been clearly demonstrated. The compounds 6-gingerol and 6-shogaol have been shown to have a number of pharmacological activities, including antipyretic, analgesic, antitussive and hypotensive effects (Sharma, 1997; Chang, 1998).

Withania somnifera **(L.) Dunal**

It consists of dried roots and root stack of Aswagantha. The main constituents of ashwagandha are alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudotropine, cuscohygrine, anferine and anhydrine. Two acyl steryl glucoside viz. sitoindoside VII and sitoindoside VIII have been isolated from root. The leaves contain steroidal lactones, which are commonly called withanolides. The withanolides have C28 steroidal nucleus with C9 side chain, having six membered lactone rings. Ashwagandha is reported to have anti-carcinogenic effects in animal and cell cultures by decreasing the expression of nuclear factor-kappaB, suppressing intercellular tumor necrosis factor, and potentiating apoptotic signalling in cancerous cell lines (Gennaro and Willium, 2000; Ryffel *et al*., 1999; Bertchinger and Himmelamann, 1997; Visen *et al*., 1996).

Astragalus membranaceus **(Fisch.) Bunge**

Its main constituents include polysaccharides, saponins, flavonoids, aminoacids, and trace elements. Research shows *Astragalus* root stimulates the immune system in many ways. It has been identified as glucans, and polysaccharide D as a hetero polysaccharide increases the number of stem cells in bone marrow and lymph tissue and encourages their development into active immune cell. It appears to help trigger immune cells from a “resting” state into heightened activity. One study showed *Astragalus* root helps promote and maintain respiratory health. It also enhances the body’s production of immunoglobulin and stimulates macrophages. *Astragalus* can help activate T-cells and natural killer (NK) cells. Several studies also show *Astragalus* proffers heart-protecting effects, including protection against oxidative damage (Boswell, 2006; Nousari and Anhalt, 1999; Kirchner *et al*., 2004).

Mechanism of action of the immunomodulators:

It has been reported that medicinal plants are rejuvenators, nutritional supplements and possess strong antioxidant activities. They also exert antagonistic action on oxidative stressors, giving rise to the formation of different free radicals. They are used mainly to combat the effects of ageing, atherosclerosis, cancer, diabetes, rheumatoid arthritis, autoimmune disease and Parkinson’s disease. Mechanisms of immunomodulation activity occur mainly via phagocytosis stimulation, macrophages activation, immunostimulatory effect on peritoneal macrophages, lymphoid cells stimulation, cellular immune function enhancement and nonspecific cellular immune system effect, antigen-specific immunoglobulin production increase, increased nonspecific immunity mediators and natural killer cell numbers, reducing chemotherapy-induced leukopenia, and increasing circulating total white cell counts and interleukin-2 levels. There are many medicinal plants which exert immunomodulatory activity in experimental models at a particular dose. Different types of screening methods both *in vivo* and *in vitro* have been employed to determine their pharmacological activity. Some medicinal plants may stimulate the immune system, (e.g., *Panax ginseng*, *Ocimum sanctum*, *Tinospora cordifolia*, and *Terminalia arjuna*), and some may suppress the immune response (*Alternanthera tenella*). Also, various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols) exhibit a wide range of immunomodulating activity (Dinesh Kumar *et al*., 2012).

Plants for Anti-tuberculosis

The recent observations of comparatively low death rate was attributed towards administration of BCG vaccination among Indian population and basis this medicinal plants advocated against Tuberculosis were screened, which can also be beneficial against Covid 19. Tuberculosis is a highly infectious disease with about one third of the world’s population including 40 % from India estimated to be infected it. However, this problem has become serious as *Mycobacterium tuberculosis* developed resistance against both the first line as also the second line drugs. Due to this, there is emergence of multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains of *M. tuberculosis* all over the world including India (Agarwal, 2004; Singh, 2007). Medicinal plants offer a great hope to fulfill these needs and have been used for curing diseases for many centuries. These have been used extensively as pure compounds or as a crude material. Only a few plant species have been thoroughly investigated for their medicinal properties (Heinrich and Gibbons, 2001). India is one of the few countries in the world which has unique wealth of medicinal plants and vast traditional knowledge of use of herbal medicine for cure of various diseases (Gupta and Tandon, 2004; Sharma, 1998). So far, few plants have been tested against mycobacteria and a few plants which showed anti-TB activity were *Salvia hypargeia*, *Euclea natalensis*, etc. (Gautam *et al*., 2007; Newton *et al*., 2000; Newton *et al*., 2002; Ulubelen *et al*., 1988; Lall and Meyer, 2001).

Medicinal plants such as *Acalypha indica*, *Adhatoda vasica*, *Allium cepa*, *Allium sativum* and *Aloe vera* were observed to have anti-tuberculosis activity against two MDR *M. tuberculosis* isolates and drug-susceptible reference strain *M. tuberculosis* H37Rv and poor/no activity against rapid grower *M. fortuitum* (TMC-1529). These MDR isolates were earlier found to be resistant against rifampicin and isoniazid, in addition to some other first line and second line drugs. As inhibition of growth by these extracts was observed in both the systems, inference about their anti-tuberculosis activity appears to be meaningful. However, more studies using more isolates/strains of *M. tuberculosis* as well as fractions of crude extract/ purified/semi-purified principles of the above plants are needed to conclude about the antituberculosis potential and promise of these plants for their ultimate use in the treatment of drug resistant tuberculosis.

In vitro anti-tubercular activity of five medicinal plants viz., *Syzygium aromaticum, Piper nigrum, Glycyrrhiza glabra, Aegle marmelos* and *Lawsonia inermis.* Solvent extracts of *Syzygium aromaticum, Piper nigrum, Glycyrrhiza glabra, Aegle marmelos* and *Lawsonia inermis* were tested against *Mycobacterium tuberculosis* H37Rv strain using Microplate Alamar Blue Assay. Activity in MABA was evaluated by lowest concentration of sample that prevents color change to pink. Extracts of all the five plants *Syzygium aromaticum, Piper nigrum, Glycyrrhiza glabra, Aegle marmelos* and *Lawsonia inermis* exhibited anti-tuberculosis activity, the proportion of inhibition of these plants extracts for *M. tuberculosis* H37Rv, inhibition was found to be 0.8µg/ml, 50µg/ml, 12.5µg/ml and 50µg/ml respectively (Renu Gupta *et al*., 2010; Rajandeep Kaur and Harpreet Kaur, 2015).

ACE/ACE2 inhibitors:

As a transmembrane protein, ACE2 serves as the main entry point into cells for some coronaviruses, including HCoV-NL63, SARS-CoV (the virus that causes SARS) (Fehr and Perlman, 2015) and SARS-CoV-2 (Li, 2013) the virus that causes COVID-19) (Zhou *et al*. 2020; Xu *et al*., 2020; Lewis, 2020). More specifically, the binding of the spike S1 protein of SARS-CoV and SARS-CoV2 to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes located within cells. This entry process also requires priming of the S protein by the host serine protease TMPRSS2, the inhibition of which is under current investigation as a potential therapeutic *(*Wang *et al*., 2008; Millet and Whittaker, 2018).

ACE/ACE2 inhibitors from plant sources and their activity:

***Allium sativum* L.**

Animal experiments showed that administration of S-allyl cysteine and captopril can synergistically reduce BP via inhibition of ACE (Shouk *et al*., 2014). Sharifi *et al*., (2003) also demonstrated ACEI effects of allicin in reduction of blood pressure. Oboh *et al*. (2013) studied the effect of phenolic extract of garlic on BP and reported that it can strongly act as an inhibitor of ACE, *in vitro*. In this study, evaluation of the free and bound phenolic inhibitory effects on ACE revealed that bound phenolics have more potent effect than the free phenolics in reduction of ACE activity; however, both inhibited malondialdehyde production (Asdaq and Inamdar, 2010) in a dose-dependent manner (Oboh *et al*., 2013).

***Cinnamomum zeylanicum* Blume**

A methanol extract of *C. zeylanicum* inhibited ACE in experimental animals (Barbosa-Filho *et al*., 2006). The anti-hypertensive mechanism was speculated to be mediated through elevation of endothelial NO and activation of the K-ATP channel in vascular smooth muscle (Nyadjeu *et al*., 2011). Ranjini et al., determined the inhibitory effects of methanolic extract of *C. zeylanicum* on ACE activity in sheep tissues. In the presence of the extract, tissue ACE activity was reduced and these effects were more significant in the kidney than in the testis and lung tissues (Ranjini *et al*., 2016).

***Jasminum grandiflorum* L.**

Arun *et al*., (2016) reported the half maximal inhibitory concentration (IC_{50}) values of jasmine to be 26-36µM. The IC_{50} values for ACE inhibition of secoiridoid aglycones of jasmine were 20-25µM (Kiss *et al*., 2008). Patten *et al.* reported relatively high ACE inhibitory activity) IC50 30µM for Sambacein I-III isolated from *J. grandiflorum* (Patten *et al*., 2016).

***Tribulus terrestris* L.**

Sharifi *et al*., (2003) in their evaluation of an aqueous extract of *T. terrestris* suggested that the BP lowering effect of the extract resulted from its ACE inhibitory activity. Anethnopharmacological investigation on Indian medical herbs reported ACE inhibitory activities for aqueous, ethanol and acetone extracts of *T. terrestris* (aerial parts). The inhibitory effect was dependent on the type of the extract with the aqueous extract having the highest ACEI activity (Somanadhan *et al*., 1999).

***Vaccinium myrtillus* L.**

Persson *et al*., (2009) in their study on bilberry and its polyphenols, incubated the endothelial cells isolated from umbilical veins with bilberry 25E extract (containing the chloride salt of the anthocyanidins and myrtillin chloride) for 10 min. The results showed that *V. myrtillus* extract (0.0062, 0.0125, 0.025, 0.05 and 0.1mg/ml) could inhibit ACE activity in a dose-dependent manner. Proanthocyanidins (e.g. tannins) isolated from bilberry decreased fluid retention, inhibited the renin-angiotensin-aldosterone system and induced an anti-hypertensive effect. In a randomized placebo-controlled clinicaltrial on71 participants, two portions of berries were consumed daily by 35 participants for 8 weeks. Berry consumption reduced SBP by about 1.5mmHg

(Cravotto *et al*., 2010).Moreover, treatment of spontaneously hypertensive stroke-prone rats with 3% blueberries for 2 weeks, decreased the level of ACE activity in the blood. However, it had no effect on ACE activity in the testis, lung, kidney or aorta (Wiseman *et al*., 2010).

***Vitis vinifera* L.**

Various studies reported the anti-hypertensive effects of grape potentially through ACE inhibition (Godse *et al*., 2010; Borde *et al*., 2011; Afonso *et al*., 2013). The antihypertensive and antioxidant effects were observed after chronic administration of myricetin (100 and 300mg/kg, per oral, for 4 weeks) –an important flavonol of grapes - to deoxycorticosterone acetate - induced hypertensive rats. Following myricetin treatment using strips of ascending colon, the cumulative concentration-response curve of angiotensin II and serotonin shifted to right (Borde *et al*., 2011).

Zinc:

Zinc is an essential trace element for plant growth and also plays an important role in various cell processes including normal growth, brain development, behavioral response, bone formation and wound healing. Zinc deficient diabetics fail to improve their power of perception and also cause loss of sense of touch and smell (Hunt, 1994). Recent studies on Covid-19, management clearly evaluated the benefit of Chloroquine derivatives when supplemented with Zinc, were able to enhance the activity by penetrating the cell membrane. Based on this the search was done. The dietary limit of Zn is 100 ppm (Jones, 1987). Along with Chloroquine it is proved that it penetrates the protein layer and inhibits the viral multiplication. The plants dealt in Table **4** clearly shows the zinc content in each plant which can be utilized along with the drug in treating Covid and also to improve the general health.

Plants with Vitamin C:

Vitamin C is available in abundance in many natural sources, including fresh fruits and vegetables. Further this is also beneficial in improving the immunity and also the status of health, which is also very important in Covid-19 management. The intestinal absorption of iron is greatly increased by adequate Vitamin C. Vitamin C is present in most fresh fruits and vegetables (Dunne, 1990). It has been established that oxidative stress is among the major causative factors in the induction of many chronic and degenerative diseases including atherosclerosis, ischemic heart disease, ageing, diabetes mellitus, cancer, neuro degenerative diseases, immuno suppression and others (Squadriato and Pelora 1998; Shahidi and Wansundhara 1992). Vitamin C is essential for humans because it has several critical functions as an enzyme Co factor; Vitamin C is involved with collagen synthesis, carnitine synthesis, converting dopamine to noradrenalin, Cholesterol metabolism. Vitamin C is a potent electron donor and reducing agent and also acts as water soluble antioxidant; Vitamin C helps to maintain DNA, proteins, lipids, enzymes and other antioxidants in their normal form. It does this by scavenging oxygen and nitrogen radicals and reducing metal ions (Carr and Feri, 1999).

Table 4. Plants rich in Zinc :

S.No.	Botanical Name	Parts Used	Zinc content (ppm)	Reference
1	*Alpinia calcarata* Roscoe	Rhizome	13.061	Ponmari *et al*., (2017)
2	*Acalypha indica* L.	Leaves	47.18	Moscow *et al*., (2012)
3	*Achyranthes aspera* Linn.	Roots, Stem & Leaves	3.523	Saraf and Samant, (2013)
4	*Azadirachta indica* Juss	Leaves	43	Kashif and Ullah, (2013)
5	*Centella asiatica* L.	Leaves	71.835	Ponmari *et al*., (2017)
6	*Enicostemma littorale* blume	Whole plant	32.87	Moscow *et al*., (2012)
7	*Glycyrrhiza glabra* L.	Root & rhizome	39.738	Ponmari *et al*., (2017)
8	*Gymnema sylvestre* R.Br.	Leaves	87.120	Ponmari *et al*., (2017)
9	*Hippophae rhamnoides* L.	Leaves	27	Kashif and Ullah, (2013)
10	*Nelumbo nucifera* Gaertn.	Flower	45.00	Moscow *et al*., (2012)
11	*Ocimum tenuiflorum* L.	Whole plant	36	Kashif and Ullah, (2013)
12	*Punica granatum* L.	Fruit	14	Kashif and Ullah, (2013)
13	*Solanum trilobatum* L.	Leaves	40.850	Ponmari *et al*., (2017)
14	*Sphaeranthus indicus* Linn.	Whole plant	38.14	Moscow *et al*., (2012)
15	*Withania somnifera* (L.) Dunal	Root	43.01	Moscow *et al*., (2012)

Table 5. Content of Vitamin C in some plants / foods (Anonymous, 2019) **:**

Sl. No.	Botanical Name	Common Name	Content of Vitamin C*
1	*Terminalia ferdinandiana* Exell	Kakadu plum	3100
2	*Myrciaria dubia* (Kunth) McVaugh	CamuCamu	2800
3	*Rosa canina* L.	Rose hip	2000
4	*Malpighia emarginata* DC	Acerola	1600
5	*Hippophae rhamnoides* L.	Seabuckthorn	695
6	*Ziziphus jujuba* Mill	Jujube	500
7	*Phyllanthus emblica* Linn.	Indian gooseberry	445
8	*Adansonia digitate* L.	Baobab	400
9	*Ribes nigrum*L.	Blackcurrant	200
10	*Capsicum annum* L.	Red pepper	190
11	*Petroselinum crispum* (Mill.) Nym. ex A.W. Hill	Parsley	130
12	*Psidium guajava* L.	Guava	100
13	*Actinidia deliciosa* (A.Chev.) C.F. Liang & A.R.Ferguson	Kiwifruit	90
14	*Brassica oleracea* L. *var. italica*	Broccoli	90
15	*Rubus × loganobaccus* L.H. Bailey	Loganberry	80
16	*Ribes rubrum* L.	Redcurrant	80
17	*Brassica oleracea* L. *var. gemmifera* DC	Brussels sprouts	80
18	*Lycium barbarum* L.	Wolfberry	73
19	*Litchi chinensis* Sonn.	Lychee	70
20	*Rubus chamaemorus* L.	Cloudberry	60
21	*Sambucus spp.*	Elderberry	60
22	*Diospyros kaki* L.	Persimmon	60
23	*Carica papaya* L.	Papaya	60
24	*Fragaria × ananassa* Duchesne.	Strawberry	60
25	*Citrus × sinensis* L.	Orange	50
26	*Citrus × limon* (L.)	Lemon	40
27	*Cucumis melo var. cantalupensis* Ser.	Cantaloupe	40
28	*Brassica oleracea* L. *var. botrytis*	Cauliflower	40

* Results are expressed in mg/ 100 gm

The content of Vitamin C in various plants above 40 mg are dealt in Table 5. Vitamin C helps to improve the immunity and also assist in various other ailments which could also support the health in managing CoV.

DISCUSSION AND CONCLUSION

Herbal remedies have long been used to treat infections and viruses, such as the common cold, influenza, fever, and even herpes. Studies have reported the inhibitory effects of medicinal plants extracts on the replication of several viruses. Particularly herpes simplex virus type 2 (HSV-2) (Debiaggi *et al*., 1988), HIV (Asres and Bucar, 2005; Vermani and Garg, 2002), hepatitis B virus (HBV) (Huang *et al*., 2006; Kwon *et al*., 2005), and emerging viral infections associated with poxvirus and severe acute respiratory syndrome (SARS) virus (Kotwal *et al*., 2005) were strongly inhibited by various plants extracts. Most of these studies have utilized either water soluble or alcoholic extracts of medicinal plants, and limited efforts have been directed toward the identification of active natural ingredient exhibiting antiviral effects. Moreover, recent studies showing antiviral potential of plant extracts against viral strains resistant to conventional antiviral agents (Serkedjieva, 2003; Tolo *et al*., 2006) have challenged the modern drug discovery practices, and deem a very careful look towards exploring natural antiviral components of medicinal plants. Some are thought to enhance the immune system and put the body in a healthier position to fight infections. Others are believed to be powerful antivirals that block certain viruses from replicating in the body. Based on the study this could lead to development of a novel drug / molecule which would be beneficial against SARS-CoV2, with special emphasis on the mode of action in order to enhance and fasten the search of a new drug in the management of this pandemic spread and also will throw a light on evolving new strategies in drug development, which are the need of this hour to treat SARS-CoV2.

Acknowledgments
The authors are grateful to Mr. V.S. Pradeep (Chairman & Managing Director) and Mrs. Jayadevi Pradeep (Director) from Cholayil Private Limited for their constant support and encouragement.

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