

REVIEW

Herbs, Immunity and nCOVID-19: Old performers in new Pandemic

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Abstract: The novel coronavirus (nCOVID-19) has spread to endless nations and turn out to be a pandemic around the globe. Because of the developing number of affirmed cases and open public hazard owing to its high risk of infection rate, it has expected a lot of consideration from world health organizations and national health regulatory and monitoring agencies. The world is in surge to explore or discover novel treatment options and vaccine that can lead to cure. There is no proven effective treatment for nCOVID-19 however along with available antiviral therapy Chinese researchers recommended herbal treatments as effective and alternative treatments options to treat this pandemic. Herbal products are wealthy in dynamic phytochemicals, such as the terpenoids, various collection of flavonoids, sulfides, lignans constituents, coumarins concentrates, saponins moities, polyphenolics composite, numerous alkaloids, polyines, furyl mixtures, proteins and related compounds, thiophenes and peptides groups. In this review we discussed pathogeneis, immunity and current herbal treatment strategies of nCOVID-19 to cure this world wide pandemic.

Keywords: Novel coronavirus (nCOVID-19), pandemic, pathogenesis, immunity, herbs.

INTRODUCTION

The 2019-2020 novel coronavirus (nCOVID-19) pandemic was initially announced in December 2019 in Wuhan province, China. This epidemic sooner proclaimed as a general public crisis at global level by the World Health Organization, related with significant severity and proportionate mortality. nCOVID-19 is hereditarily identified and resembled with SARS-CoV, which was known as worldwide pandemic with 1,934,986 affirmed cases and 120,438 deaths in more than 25 countries with 456,841 recovered patients (Takeshi *et al*, 2020). Corona infectivity has been considered as a kind of self-restricting infectious disorder, and most cases with minor manifestations can recoup in within 14 days. Severe cases represents cough, difficulty in breathing, pneumonia, coarse breathing sounds of both lungs with high grade fever (Verity *et al*, 2020). This virus targets the human respiratory system. (Zhu *et al*, 2020) and has human-specific transmission that spreads principally through infected patient droplets, saliva, nasal discharge produced during sneeze and cough. An infected person shows mild to moderate symptoms of cough, fever, GI disturbances and dyspnea (Verity *et al*, 2020). A person can prevent from nCOVID-19 via segregation of patients in a quarantine up to 14 days, by washing hands, using sanitizers and N95 masks (Lu *et al*, 2020; Wan *et al*, 2020). There is no specific treatment of nCOVID-19 thus special protective or reducing purposes of transmission should be applied on a state level to the individual's involved (Li *et al*, 2020).

This pandemic is being spread in all over the world and the collective figures of established cases in world has reached 1,118,601 accompanied by cured cases 229,278 and deaths as of 3rd April 59,226 (WHO, 2020) however still the treatment option are question mark and scientist or health officials are continuous searching an effective cure to treat nCOVID-19 but not yet to be developed. Some of the doctor in China as well as in Europe investigated potential combinations include of protease inhibitor lopinavir/ritonavir, which is commonly used to treat human immunodeficiency virus (HIV), for the treatment of COVID-19-infected patients (Lu, 2020; Zumla *et al*, 2016). Similarly other reported nucleoside analogues, neuraminidase inhibitors, remdesivir, umifenovir, tenofovir antiviral treatments for nCOVID-19 pandemic. Some practices revealed chloroquine phosphate can be a good option, that can relieves the symptoms for most patients and accelerates virus sero-conversion (Touret *et al*, 2020; Ren *et al*, 2020; Savarina *et al*, 2006). Chinese researchers believed a healthy immune system can counteract pathogens in body, including viruses that can make us sick, additionally strong immunity will likely generate a more robust antibody response that gives more protection against the nCOVID-19 virus (Li & Peng, 2013; Leung, 2007). China have faced worsen pandemic situation before one month since December 2019 to March 2020, a number of clinical trials in china pandemic showed that traditional Chinese medicine take significant part to treat nCOVID-19 infection and conveying new expectation for the prevention and control to this pandemic (Yang *et al*, 2020; Burki, 2020; Ul Qamar *et al*, 2020). In this review we have focused on the role of herbal medicines in

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immunity and we reviewed some herbal combinations against the treatment of nCOVID-19 pandemic.

Pathogenesis of nCOVID-19

nCOVID-19 is a serious and fatal infectious disease caused by SARS coronavirus (SARS-Cov 2), a novel human coronavirus. SARS infection sometimes symptomatic and a symptomatic, common symptoms are cough, fever, dyspnea, diarrhea and myalgia (Huang *et al*, 2020). Severity of infection represents pneumonia and other system organ loss. Recent case studies of nCOVID-19 patient's disease model suggested that, it cause its pathogenesis in triple phases model that starts from replication of viral material, hyperactivity based immune response, and destruction of pulmonary path (Weiss *et al*, 2005). Virus enter into the respiratory tract and connect to explicit receptor of cellular range by means of the spiking part of protein in to the epithelial cells then released its RNA genome into the cytoplasm. Viral attachment to host activates a conjugational change in the part of spike protein that starts synthesis of a protein from an mRNA template which is translation process, after translation viral genome begins to replicate (Li *et al*, 2020). After rapid replication of nCOVID-19 the virion spike proteins attached to the multitude receptor known as angiotensin-converting enzyme II. Alveolar cells based on lung epithelium is the main origion of these cellular part of receptors, nCOVID-19 use these receptors to enter into target cells (Zou *et al*, 2020; Chan *et al*, 2020). After alveolar damage in severe infection nCOVID-19 may be infected different organs, including intestines, kidneys, brain, and several types of immune cells (Chan *et al*, 2020; Gu, *et al*, 2007). Current data revealed the presence of reduced leukocyte count (marked leukopenia), raised C reactive proteins and increased levels of cytokines in moderate to severe patients (Rothan *et al*, 2020; Li *et al*, 2020). Similarly Considerable higher blood levels of cytokines (IL1- β , IL7-10, IL1RA, vital FGF2, GMCSF, GCSF, IFN γ , MCP1, IP10, MIP1 α & β , PDGFB, VEGFA and TNF α ,) were noted in patients diagnosed positive with nCOVID-19 infection and considered as the major stimulus of disease propagation and severity (Wang *et al*, 2020; Rothan *et al*, 2020). nCOVID-19 infection stimulates cytokines expression radically, and T lymphocytes and their subsets CD4(+) and CD8(+) T cells are decreased after onset of the disease which accelerate inflammation in lungs and reasoned for pneumonia (Li *et al*, 2020).

nCOVID-19 and Immunity

Human immune host cells recognize the invasion of viruses and mount strong antiviral responses. Viruses when enter in human body, initially activate the innate immune system that provides an imminent but incomplete defense against a foreign insult, it recognizes viral components through pattern-recognition receptors (PRRs) (Takeuchi and Akira, 2009). Viral genomic DNA, single-

stranded RNA, double-stranded RNA are detected via host PRRs (Akira *et al*, 2006; Beutler *et al*, 2007). There are three types of PRRs such as toll-like receptors (TLRs), retinoic acid-inducible gene I like receptors (RLRs) and nucleotide oligomerization domain like receptors (NLRs) that are implicated in the recognition of viral components and significant for producing number of interferons (IFNs), interleukins & cytokines (Kanneganti *et al*, 2007). After that the adaptive immune response become initiated which is an antigen-specific system that includes long-lived lymphocytes (memory cells) and their highly specialized receptors. (Pancer & cooper, 2006). Host body consequently initiates the humoral and cellular immunity, which are mediated by virus particular B and T cells. Similar to common acute viral infections, the antibody profile against nCOVID-19 virus has a typical pattern of IgM and IgG production (Li *et al*, 2003). The nCOVID-19-specific IgM antibodies vanish after 4 months, however the IgG antibody can retain for life time that indicates IgG antibody may primarily carry out a defensive role against nCOVID-19 (Xu *et al*, 2020). The latest finding on nCOVID-19 mediated cellular immunity displays the reduced number of T helper and killer cells (CD4+ & CD8+) in the peripheral blood of nCOVID-19-infected patients (Diao *et al*, 2020; Li *et al*, 2020). In the acute phase response nCOVID-19 patient's blood showed decrease T lymphocyte cells but after chronic inflammation T cells expression become raised even if there is no antigen, memory and helper T cells can last for 4-5 years in nCOVID-19 recovered persons (Fan *et al*, 2009). These findings may be helpful in future for the designing of appropriate antiviral drugs or vaccines against nCOVID-19.

Both innate and adaptive immune systems diligently work together in a modified-tuning manner (Zu *et al*, 2020). Subsequently entering into the host , nCOVID-19 virus hijacking the cell's metabolic machinery to produce copies of itself that may burst out of infected cells in the air way. Host immune system produces interferon, interleukins and other cytokines that involve in eradicating viral constituents from infected cells. These immune cells than start killing of viruses and its components and results in viral resistance on uninfected cells (Catanzaro *et al*, 2020). Cytokines and other inflammatory mediators like prostaglandins and interleukins are also precarious not only for eradicating viral infection but also evoking inflammation and recruiting innate and acquired immune cells in the host (Takeuchi & Akira, 2009). In acute phase raised levels of cytokines initiated lysis of viruses via activation of caspases to induce apoptosis in the target thus responsible for immune response down regulation, T cell exhaustion and organ failure (Delano & Ward, 2016). Likewise in nCOVID-19 infection critical patients showed severe respiratory failure with leukocytosis and decreased T lymphocytes, impaired immune response could be the

reason of death in critical cases of nCOVID-19 infection (Conti *et al*, 2020; Huang *et al*, 2020).

Current studies suggested that nCOVID-19 infection recovery requires strong immune response to eradicate the virus and to prevent disease progression (Zu *et al*, 2020). As a result, approaches to boost immune responses at acute stage are indeed important. Therefore an autogenously protective immune response development is required in the beginning of nCOVID-19 infection. In current pandemic situation it is mandatory the host should be in good general health and dietary habits that produces specific antiviral immunity (Shi *et al*, 2020).

Herbs and Immunity

The use of the herbs as phytochemical for boosting the immune system against the pathogens (viruses and bacteria) has a traditional history. Body immune system can counter several pathogens like bacteria and viruses that can make us sick, herbs contain several active metabolites like poly phenols, saponins, alkaloids, terpenoids and some vitamins like A, B and C, as well as minerals all of that work as a immunostimulant and optimize our immunity against pathogens (Tan *et al*, 2004; Ding *et al*, 2014). To keep our immune system functioning at its best, use of the most effective herbs can minimize onset of viral infections by boosting our immunity. It is suggesting that constituents of vegetable and fruits, such as vitamins, minerals, lycopene, alkaloids, polyphenols and other phytochemicals are helpful in sustaining immune and physical functions (Lillehoj *et al*, 2018; McDermott, 2000). Herbal medicines have been used to treat the infectious diseases since ancient time, preliminary with the Asian prehistoric Ayurvedic treatment, and expanding to the various primordial Chinese forms, European and supplementary supporting systems of traditional herbs and medicines (Zhuang *et al*, 2012). The 21st century has seen interchange in the focus of pharmaceutical trials on a variety of infectious diseases by cautiously aligning the control of conventional medicines along with the modern concept of evidence based medicine, standardization and pre marketing clinical trials to maintain therapeutic efficacy (Tariq *et al*, 2019; Yang *et al*, 1999). About 50% synthetic medicines are derived from phytochemicals because they offer a rich resource of active plant derived antioxidant metabolites that boost immune system and could be a strong candidate for novel antiviral drug development. For example glycyrrhiza glabra, Acacia auriculiformis, Curcuma Longa, Citrus Lemon, Cassia fistula, zingiber officinale, Olex polyama, Pyrrosia lingua, Glycyrrhiza inflate, Lindera aggregata Senecio tenuifolius and Zingiber capitatum are herbs that have been reported for their antiviral and antibacterial activities (Lin *et al*, 2014; Cheng *et al*, 2006; Li *et al*, 2005; Ryu *et al*, 2010; Dhawan, 2012; Dao *et al*, 2010). All of the above herbal plants balance a wide range of resistant reaction at

immune level, including articulation of mucins and keratins, apoptosis, lymphopoiesis, cytokine creation, capacity of neutrophils, natural killer cell, lymphocytes T & B, macrophages or monocytes, and immunoglobulin production, thereby providing defensive immunity against viruses (Zhou *et al*, 2015; Ganjhu *et al*, 2015). Above exploration of medicinal plants and its phytochemicals provide a vision to identify new therapeutically active compounds alone and in combination to cure novel pandemics. That may be provide the way to discovering cheap, possibly safe, and also clinically advantageous remedies to assist the immune system against viral diseases. In this context it is a need of this century to identify the exact antiviral mechanism of these proposed herbal phytochemicals on viral life cycle, as well as on the targeting of virus–host particular interactions.

nCOVID-19 and Herbs

Presently, there are no specific treatment or vaccine to treat nCOVID-19 pandemic. The only option available is using immunoglobulins or plasma infusion of recovered nCOVID-19 Patients, preventive measure and supportive treatment like trial of some extended-spectrum antiviral drugs (i.e. Nucleoside analogues & HIV-protease inhibitors) on critically ill patients that could decrease viral pathogenesis till the particular antiviral becomes formulated (Lu, 2020). Currently in Wuhan city 75 patients were administered HIV protease (lopinavir 500 mg bd) and neuraminidase inhibitors (oseltamivi 75mg bd) orally along with 0.25 g ganciclovir IV up to 3–14 days (Chen *et al*, 2020; Li *et al*, 2020). Some of the patient were responded however the success rate depending upon patient's immune response. Another case study exhibited that the remdesivir which is an investigational antiviral compound undergoing clinical trials and chloroquine showed efficacious role to control nCOVID-19 infection (Singh *et al*, 2020). However it was case control study, a large cohort studies are required to further investigate the efficacy of chloroquine against nCOVID-19. Thus, this current scenario reveals there is a necessity to develop an effective vaccine and antiviral drug from herbal origin or synthetically for prophylaxis and treatment of nCOVID-19 infection (Zou *et al*, 2020). ACE II receptors are commonly the suitable candidate for drug target to prevent virus infection, the inhibitory effect of some herbal plants to this receptor suggests giving protection of the virus recognition (Utomo *et al*, 2020). A Ginger and turmeric rhizome produces a noteworthy decline in ACE and arginase triggers with a simultaneous augment in levels of nitric oxide (NO) (Akinyemi *et al*, 2016). Chang *et al* (2012) reported that fresh ginger is useful in human respiratory disorder due to syncytial virus as it promotes the plaque development in epithelium of airway and consequently blocks the viral internalization and attachment, Thus act as potent antiviral agent. Turmeric (Curcuma longa) deals to Europe and West Asia have shot up in light of the fact that its therapeutic

properties are getting restored consideration when the coronavirus is scattering widely and quickly. Ginger (*Zingiber officinale* L.) contain gingerol, shogaole, Zingiberene, phellandrene and zingerone. However the photochemical investigations show the main bioactive constituents are zingerone, paradol, gingerol and shogaol which can be derived from Ginger (Shidfar *et al.*, 2015). Goswami *et al* (2020) reported that ginger bind with high in silico affinity and could be a potent nCOVID-19 Protease Inhibitor. Similarly Khaerunnisa *et al*, 2020 assessed bioactive compounds found in medicinal plants as potential COVID-19 inhibitors, using a molecular docking study and reported that kaempferol, quercetin, luteolin-7-glucoside, curcumin, catechin, Glycyrrhizin, epicatechin-gallate, zingerol, gingerol are potential inhibitors of the COVID-19 similar to nelfinavir.

Another herb derived phytochemical (flavonoid) isolated from liquorice roots (*Glycyrrhiza glabra*,) extract to treat nCOVID-19 is diammonium glycyrrhizinate. Liquorice contain saponin, flavonoids, isoflavonoids, stilbenoids, and coumarins. In folklore medicine it has long been used to treat common respiratory ailments along with honey such as coughs, pharyngitis and sneezing as well as in maldigestion. Chinese scientist suggested combination of diammonium lcyrrhizinate along with vitamin C is a successful option to fight nCOVID-19 infection. This finding became widespread through social media and reporting in "Nature" publications (Nat. Plants 6, 177 (2020); Gupta & Mujeeb, 2018).

Protease inhibitors is also suggested to be the good drug candidate to halt the virus life cycle (Qamar *et al.*, 2020; Haider *et al.*, 2020). In the pathogenesis of nCOVID-19 Main Proteases (MPro) enzymes play very important role in the propagation of the Coronavirus pandemic (Chandel *et al*, 2020). Proteases are replication-related enzymes, they are highly sealed (Zhou *et al*, 2020). It was proposed that drugs that inhibit conserved proteases have the ability to prevent replication and proliferation of the virus by interfering with the post-translational processing of essential viral polypeptides (Zhavoronkov *et al*, 2020). Yang *et al*, 1999 reported Aeculus Chinesis is a potent antiviral agent potentially inhibits protease enzyme. Phenolic compounds of *Isatis indigotica* against SARS-CoV-2 have been reported by Lin *et al.*, 2005. Additionally Yousaf *et al* (2014) reported about citrus lemon that it had the utmost antiviral activity and could reduce viral pathogenicity up to 100 fold. Similarly Citrus Lemons are high in nutrient value including vitamin C as well, a characteristic immune booster agent which improves the safe framework and has strong antiviral and antibacterial characters by supporting the invulnerable immune system, prevents bacterial growth and infections, treat throat infections (from the common cold to tonsillitis) (Chiesa *et al*, 2019; Makni *et al*, 2018).

One more herbal seed *Nigella sativa* L. is one of the most important herb in folklore medicine as its seeds contains longifolene, Thymoquinone, thymohydroquinone, α -thujene and p-cymene. Several rearches has demonstrated its antibacterial, antifungal and antiviral activities (Ulasli *et al*, 2014; Aqil *et al*, 2018). Currently Bouchentouf and Missoum, (2020) reported in their molecular docking study that Nigellidine from the *Nigella sativa* appeared to have the best potential to act as antiviral against nCOVID-19 treatment.

China has one of the world's oldest medical system (Traditional Chinese medicines) that is based on its traditional herbal medicine. In current pandemic situation Chinese herbal decoctions are openly recommended to nCOVID-19 patients along with antiviral therapy (Lu, 2020). A number of patent herbal drugs, such as Huoxiang Zhengqi, Lianhua Qingwen and Radix isatidis capsules, are being proposed as treatments (Ren *et al*, 2020; Xu *et al*, 2020). According to their experts these phytomedicines have been very useful in managing nCOVID-19 symptoms such as sneezing, cough, lethargy, gastrointestinal related problems and beside relieving dyspnea (Ni *et al*, 2020). Despite all of the above herbal remedies other phytochemical also have active ingredients particularly flavonoids that are to a great extent viewed as gainful for human wellbeing against contamination and other ailment avoidance. As a class of nontoxic and successful characteristic natural remedies, traditional medications could be eventual fate of this world in near future as transformational approach (Zhang *et al*, 2020). Conversely, it will be far to additionally validate, approve and elucidate the attributable pharmacological activity and develop new herbal antiviral drugs.

RECOMMENDATIONS

To study all available scientific data on nCOVID-19 treatment and after reviewing patient's disease states in different countries we have concluded that the herbal remedies and decoctions are very beneficial to boost host immune response against COVID-19 viral infection. Natural diet modulate our immune response that often been destabilized by inadequate nutritional state. Moreover, the wholesome status of the host, ought to be considered as a contributing variable to the rise of viral infectious diseases. Hence, we recommend that the assessment of individuals nutritional status of nCOVID-19 infected patients prior to administer the specific treatment is necessary and adding together of herbal remedies or decoction along with treatment as china did may give successful eradication of this pandemic. We should take fresh turmeric, *nigella sativa* in our daily meals and a decoction of *Glycyrrhiza glabra* L. ginger and lemon for improving immunity during the Coronavirus Disease (nCOVID-19) Outbreak. We believed that the different combinations of herbs with

multifaceted mechanism appear to be synergistic to attain desired therapeutic effects.

REFERENCES

- Akinyemi AJ, Thome GR, Morsch VM, Stefanello N, da Costa P, Cardoso A and Schetinger MRC (2016). Effect of dietary supplementation of ginger and turmeric rhizomes on ectonucleotidases, adenosine deaminase and acetylcholinesterase activities in synaptosomes from the cerebral cortex of hypertensive rats. *J. Appl. Biomed*, **14**(1): 59-70.
- Akira S, Uematsu S and Takeuchi O (2006). Pathogen recognition and innate immunity. *Cell*, **124**(4): 783-801.
- Aqil K, Khan MUR, Aslam A, Javeed A, Qayyum R, Yousaf F and Umar S (2018). *In vitro* Antiviral Activity of *Nigella sativa* against Peste des Petits Ruminants (PPR) virus. *Pak. J. Zool.*, **50**(6): 2223-2228.
- Arashiro T, Furukawa K and Nakamura A (2020) COVID-19 in 2 persons with mild upper respiratory tract symptoms on a cruise ship, Japan. *Emerging Infect Dis*, **26**(2): 6.
- Beutler B, Eidenschenk C, Crozat K, Imler JL, Takeuchi O, Hoffmann JA and Akira S (2007). Genetic analysis of resistance to viral infection. *Nat. Rev. Immunol.*, **7**(3): 753-676.
- Bouchentouf S and Missoum N (2020): Identification of compounds from *Nigella sativa* as new potential inhibitors of 2019 novel coronasvirus (Covid-19): Molecular docking study. *ChemRxiv*. 12055716.
- Burki TK (2020). Coronavirus in China. *The Lancet. Respiratory Medicine*, **8**(3): 238.
- Catanzaro N and Meng XJ (2020). Induction of the unfolded protein response (UPR) suppresses porcine reproductive and respiratory syndrome virus (PRRSV) replication. *Virus Research*, **276**(15): 197820.
- Chan JF, Kok KH, Zhu Z, Chu H, To KK and Yuen S and Yuen KY (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg. Microbes Infect.* **9**(1): 221-36.
- Chandel V, Raj S, Rathi B and Kumar D (2020). *In silico* identification of potent COVID-19 main protease inhibitors from FDA approved antiviral compounds and active phytochemicals through molecular docking: A drug repurposing approach. *Chem. Biol. Lett.*, **7**(3): 166-175.
- Chang JS, Wang KC, Yeh CF, Shieh DE and Chiang LC (2013). Fresh ginger (*Zingiber officinale*) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *J. Ethnopharmacol.*, **145**(1): 146-151.
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study, *Lancet*, **395**(10223): 507-513.
- Chiesa MA, Roeschlin RA, Favaro MA, Uviedo F, Beneyto LC, D'Andrea R, Gadea J and Marano MR (2019). Plant responses underlying nonhost resistance of *Citrus limon* against *Xanthomonas campestris* pv. *campestris*. *Molecular Plant Pathology*, **20**(2): 254-69.
- Conti P, Ronconi G, Caraffa AL, Gallenga CE, Ross R, Frydas I and Kritas SK (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. *J. Biol. Regul. Homeost. Agents*, **34**(2): 1.
- Dao TT, Nguyen PH, Lee HS, Kim E, Park J, Lim SI et al (2011). Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from *Glycyrrhiza inflata*. *Bioorg. Med. Chem. Lett.*, **21**(1): 294-298.
- Delano MJ and Ward PA (2016). The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunological Reviews*, **274**(1): 330-353.
- Dhawan BN (2012). Anti-viral activity of indian plants. *Proceedings of the National Academy of Sciences, India. Section B.*, **82**(1): 209-224.
- Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L and Yuan Z (2020). Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Medrxiv*.
- Ding W, Gu J, Cao L, Li N, Ding G, Wang Z, Chen L, Xu X and Xiao W (2014). Traditional Chinese herbs as chemical resource library for drug discovery of anti-infective and anti-inflammatory. *J. Ethnopharmacol.* **155**(1): 589-598.
- Fan YY, Huang ZT and Li L et al (2009). Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. *Arch. Virol.*, **154**(7): 1093-1099.
- Ganjhu RK, Mudgal PP, Maity H, Dowarha D, Devadiga S, Nag S and Arunkumar G (2015). Herbal plants and plant preparations as remedial approach for viral diseases. *Virusdisease*, **26**(4): 225-236.
- Goswami Dibakar, Kumar Mukesh, Ghosh Sunil K and Das Amit (2020). Natural product compounds in *Alpinia officinarum* and ginger are potent SARS-CoV-2 papain-like protease inhibitors. *Chem. Rxiv*. Preprint, pp.139656.
- Gu J and Korteweg C (2007). Pathology and pathogenesis of severe acute respiratory syndrome. *The Am. J. Pathol.*, **170**(4): 1136-1147.
- Gupta T and Mujeeb M (2018). Ammonium glycyrrhizinate: A comprehensive review of its traditional use, phytochemistry, pharmacology & safety. *AJPER*, **7**(1): 58-65.
- Haider Z, Subhani MM, Farooq MA, Ishaq M, Khalid M, Khan RSA and Niazi AK (2020). *In silico* discovery of novel inhibitors against main protease (Mpro) of SARS-CoV-2 using pharmacophore and molecular docking base. Preprints.

- Huang C, Wang Y, Li X, Ren L, Zhao J and Hu Y (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, **395**(15): 497-506.
- Kanneganti TD, Lamkanfi M and Nunez G (2007). Intracellular NOD-like receptors in host defense and disease. *Immunity*, **27**(4): 549-559.
- Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S and Soetjipto S (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. Prepr. pp.1-14.
- Leung PC (2007). The efficacy of Chinese medicine for SARS: A review of Chinese publications after the crisis. *Am. J. Chin. Med.*, **35**(04): 575-581.
- Li G, Chen X and Xu A (2003). Profile of specific antibodies to the SARS-associated coronavirus. *N. Engl. J. Med.*, **349**(5): 508-509.
- Li G, Hu R and Zhang X (2020). Antihypertensive treatment with ACEI/ARB of patients with COVID-19 complicated by hypertension. *Hypertens Res.*, pp 1-3.
- Li SY, Chen C, Zhang HQ, Guo HY, Wang H, Wang L (2005). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antivir. Res.*, **67**(1): 18-23.
- Li T and Peng T (2013). Traditional Chinese herbal medicine as a source of molecules with antiviral activity. *Antiviral Res.*, **97**(1): 1-9.
- Lillehoj H, Liu Y, Calsamiglia S, Fernandez-Miyakawa, ME, Chi F, Cravens RL, Oh S and Gay CG (2018). Phytochemicals as antibiotic alternatives to promote growth and enhance host health. *Vet. Res*, **49**(1): 76.
- Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L and Ho TY (2005). Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. *Antivir. Res.*, **68**(1): 36-42.
- Lu, H. (2020). Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Bioscience Trends*, **14**(1): 69-71.
- Makni Mohamed *et al* (2018). *Citrus limon* from Tunisia: phytochemical and physicochemical properties and biological activities. *BioMed Res. Int*, 6251546.
- McDermott JH (2000). Antioxidant nutrients: Current dietary recommendations and research update. *J. Am. Pharm. Assoc. (Wash)*, **40**(6): 785-799.
- Ni L, Zhou L, Zhou M, Zhao J and Wang DW (2020). Combination of western medicine and Chinese traditional patent medicine in treating a family case of COVID-19 in Wuhan. *Frontiers of Medicine*, 1-5.
- Pancer Z and Cooper MD (2006). The evolution of adaptive immunity. *Annu. Rev. Immunol.*, **24**(1): 497-518.
- Qamar MT, Alqahtani SM, Alamri MA and Chen L (2020). Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Preprints.
- Qamar MT, Alqahtani SM, Alamri MA and Chen LL (2020). Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *J. Pharm. Anal.*, **9**(3): 22-26.
- Redeploying Plant Defenses (2020). *Nature Plants*, **6**(3): 177.
- Ren JI, Zhang AH and Wang XJ (2020). Traditional Chinese medicine for COVID-19 treatment: *Pharmacol. Res.*, **155**(1): 104743.
- Rothan HA and Byrareddy SN (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.*, **109**: 102433.
- Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY and Kim D (2010). Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL (pro) inhibition. *Bioorg. Med. Chem.*, **18**(22): 7940-7947.
- Savarino A, Di Trani L, Donatelli I, Cauda R and Cassone A (2006). New insights into the antiviral effects of chloroquine. *Lancet Infect. Dis.*, **6**(2): 67-69.
- Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G and Melino G (2020). COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.*, **27**: 1451-1454.
- Shidfar F, Rajab A, Rahideh T, Khandouzi N, Hosseini S and Shidfar S (2015). The effect of ginger (*Zingiber officinale*) on glycemic markers in patients with type 2 diabetes. *J. Complement. Integr. Med.*, **12**(2): 165-170.
- Singh AK, Singh A, Shaikh A, Singh R and Misra A (2020). Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes Metab. Syndr.*, **14**(3): 241-246.
- Takeuchi O and Akira S (2008). Innate immunity to virus infection. *Immunol. Rev.*, **227**(1): 75-86.
- Tan BK and Vanitha J (2004). Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: A review. *Curr. Med. Chem.*, **11**(11): 1423-1430.
- Tariq S, Wani S, Rasool W, Shafi K, Bhat MA, Prabhakar A, Shalla AH and Rather MA (2019). A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens. *Microb. Pathog.*, **134**(1): 103580.
- Touret F and de Lamballerie X (2020). Of chloroquine and COVID-19. *Antiviral Res.*, **177**(3): 104762.
- Ulasli M, Gurses SA, Bayraktar R, Yumrutas O, Oztuzcu S, Igci M and Arslan A (2014). The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. *Molecular Biology Reports*, **41**(3): 1703-1711.

- Utomo RY, Ikawati M and Meiyanto E (2020). Revealing the potency of citrus and galangal constituents to halt SARS-CoV-2 Infection. *Preprints*, 2020030214
- Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, Cuomo-annenburg G, Thompson H, Walker P, Fu H, Dighe A, Griffin JT, Baguelin M, Bhatia S, Boonyasiri A, Cori A, Cucunuba Z, FitzJohn R, Gaythorpe K, Green W and Ferguson NM (2020). Estimates of the severity of coronavirus disease 2019: A model-based analysis. *Lancet Infect. Dis.*, **S1473-3099**(20): 30243-30247.
- Wan Y, Shang J, Graham R, Baric RS and Li F (2020). Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J. Virol.*, **94**(7): e00127-20
- Wang J and Tang F Wei (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, *China J. Med. Virol.*, **92**(4): 441-447.
- Weiss SR and Navas-Martin S (2005). Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. *Microbiology and molecular biology reviews*. *MMBR*, **69**(4): 635-664.
- World Health Organization (WHO), Novel Coronavirus (2019-nCoV), *WHO Bull.*, pp.1-7.
- Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Yanhong Tai Y, Bai C, Gao T, Song J, Xia P, Jinghui Dong J, Zhao J and Wang FS (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Resp. Med.*, **8**(3): 420-422.
- Yang NS, Chou CJ, Lin LC, Tsai WJ and Kuo YC (1999). Evaluation of Chinese herbs that affect the cell-mediated immunity (III). *Chin. Med.*, **10**(3): 179-188.
- Yang XW, Zhao J, Cui YX, Liu XH, Ma CM, Hattori M and Zhang LH (1999). Anti-HIV-1 protease Triterpenoid saponins from the seeds of *Aesculus chinensis*. *Jour. Nat Prod.*, **62**(1999): 1510-1513.
- Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A review and perspective. *Int. J. Biol. Sci.*, **16**(10): 1708-1717.
- Yousaf T, Rafique S, Wahid F, Rehman S, Nazir A, Rafique J and Shah SM (2018). Phytochemical profiling and antiviral activity of *Ajuga bracteosa*, *Ajuga parviflora*, *Berberis lycium* and *Citrus lemon* against Hepatitis C Virus. *Microb. Pathog.*, **118**(5): 154-158.
- Zhavoronkov A, Aladinskiy V, Zhebrak A, Zagribelnyy B, Terentiev V, Dmitry S et al. (2020). Potential COVID-2019 3C-like protease inhibitors designed using generative deep learning approaches. *ChemRxiv*. Preprint.
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, and Chen HD (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, **579**(7798): 270-273.
- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J and Niu P (2020). China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.*, **382**(8): 727-733.
- Zhuang SR, Chiu HF, Chen SL, Tsai JH, Lee MY, Lee HS and Wang CK (2012). Effects of a Chinese medical herbs complex on cellular immunity and toxicity-related conditions of breast cancer patients. *Br. J. Nutr.*, **107**(5): 712-718.
- Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z and Guo Q (2020). SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N. Engl. J. Med.*, **382**(12): 1177-1179.
- Zumla A, Chan JF, Azhar EI, Hui DS and Yuen KY (2020). Coronaviruses - drug discovery and therapeutic options. *Nat. Rev. Drug Discov.*, **15**(5): 327-347.