

Exploring Natural Compounds for Covid-19 Treatment: A Review

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ABSTRACT

Amid this covid19 pandemic, the scientist across the world are still struggling to find solutions in the form of treatment measures. Natural compounds have been found useful not only as the treatment measures for treating number of disease conditions but also as source of lead molecules. Natural compounds like colchicine were found effective against the cytokine storm. Many of the antiviral compounds are obtained initially from natural sources. Vaccine although are available as preventive measures but effectiveness of vaccines is in questions as variants of novel corona virus are on rise. Scientists across the nations may need to try the natural products from crude drugs. These natural compounds may be tested as such or their semisynthetic derivatives can be compounded and tested concerning their effectiveness in Covid19. The scientist community needs focus on the direction of trying natural compounds to combat this pandemic.

Keywords: Covid-19, Natural Compounds, SARS-CoV-1, MERS-CoV, SARS-CoV-2

I. INTRODUCTION

The twenty-first century as of now has witnessed three outbreaks of Coronavirus. The first being reported as SARS-CoV (Serious Acute Respiratory Syndrome- Coronavirus) in 2002 and second in 2012 as MERS- CoV (Middle East Respiratory Syndrome-Corona Virus). The third outbreak is most recent which was reported in December 2019 now referred to as SARS-CoV-2 (Serious Acute Respiratory Syndrome-Corona Virus-2)^[1]. The first two outbreaks were epidemics but the third one now been declared as pandemic².

It seems the virus is in the rapid evolution phase as none of the molecules is giving promising results for treating this global threat. This virus is a member of the Coronaviridae family, identified in the mid-1960s. Highly pathogenic strains of this family have emerged during the last two decades, including SARS-CoV-2, Middle East respiratory syndrome virus (MERS-CoV, 2012, Saudi Arabia),

and severe acute respiratory syndrome virus (SARS-CoV, 2002, China)³. Apart from this other human pathogenic coronavirus includes HCoV- 229E, HCoV- OC43, HCoV- NL63, and HCoV- HKU1. Coronaviruses, ranging from 60 to 220 nm in size, are enveloped single-stranded RNA viruses with crown-like spikes on their surfaces (Rosa et al., 2012)⁴. The SARS-CoV-2 has been identified as β -coronavirus, a non-segmented enveloped positive-sense RNA virus, with a 29.9 kb genome⁵. SARS-CoV-2 causes severe respiratory tract infection in humans and utilizes angiotensin-converting enzyme 2 (ACE2) receptors to infect humans⁶. The generalized symptoms of the infection are cough, cold, fever, and difficulty in breathing.

Few antiviral strategies are found working against the Novel coronavirus infection but neither one is specific. Although the trials are ongoing for developing vaccines against COVID-19, the WHO has declared that it will take another 12-18 months to develop a vaccine against the condition. Hence there is an urgent need to develop agents to treat this pandemic.

Given this, natural compounds will be a handy tool to develop antiviral agents. The scientists across the globe since the epidemics in 2002 have worked on several natural compounds and found to be effective against the coronavirus. Since there are not much of the differences in SARS-CoV and SARS-CoV-2; these compounds as such or with some modifications may work wonder to fight this pandemic. This will also pave the way as a guide regarding the future outbreaks if found effective against SARS-CoV-2. The present review is a compendium dealing with attempts to develop antiviral compounds from natural origin and reported crude drugs treating similar symptoms. This will serve a bit of purpose across the scientific community to develop a treatment for the ongoing pandemic of SARS-CoV-2.

LITERATURE SURVEY METHODOLOGY

Keeping in view the aim of this review to find out natural compounds having antiviral activity against SARS-CoV, databases used were Google scholar, Science Direct, PubMed, Traditional knowledge digital library, Marine natural Product Library etc. Primary search words used were SARS-CoV-1, SARS-CoV-2, MERS-CoV, natural products etc. On the basis of literature search the number of natural compounds were found effective particularly against SARS-CoV and MERS-CoV. The database of these compounds have been used by various authors for molecular docking on COVID-19. The number of potential compounds which may be studied for their efficacy along with their modes of action have been included in the Table I.

HISTORY IN SUPPORT OF NATURAL COMPOUNDS

Natural products in the past, in the present and the future, will act as a source of drugs for almost every indication. Most of the agents used for the treatment of bacterial and fungal infections are from natural sources for example right from antibiotics (Penicillin) to Artemether and Artemisinin. Natural products used as such or provided template molecules for the synthesis of the majority of antibacterial and antifungal drugs. However, most of the antiviral compounds today are being produced via chemical synthesis still natural products have a significant contribution to the development of the antiviral compound. Some of the natural antiviral compounds like nucleoside analogues spongouridine and spongothymidine were discovered from marine sources. DNA polymerase inhibitor, arbinosyladenine (vidarabine) was discovered from a natural source. Natural compounds like pyrazomycin or showdomycin representing structural similarity with ribavirin one of the most remarkable antiviral compounds pave the way about the importance of natural compounds as antiviral probable. Nucleoside analogue as the central theme for defeating viruses comes from natural compounds⁷.

In the context of outbreaks of Coronavirus (SARS-CoV-1), China has approved plenty of traditional herbal preparation either to treat or to alleviate the symptoms associated with SARS-CoV 1 and 2, Number products which are approved in china are polyherbal preparations which boosts up the immunity. Number of Governments across the globe are focussing on the natural immunity

booster to be included in the treatment regimen to fight against the dreaded virus-like SARS-CoV-2.

Duringtheepidemic of SARS-CoV-1 in 2002, the fatality rate reported in Hong Kong and Singapore was 18% while in China it was about 52% initially. By the date 20th May of 2003, the fatality rates were found to decrease by 4% to 1%. According to Chen et al., (2004) the reduction in fatality rates was mainly attributed to due incorporation of traditional remedies along with conventional therapy (antivirals, corticosteroids, oxygen therapy, antibiotics)⁸.

During the SARS outbreak, 1063 volunteers (926 hospital workers,37 laboratory workers) working in high-risk environments used Sang Ju Yin plus Yu Ping Feng San. None of the workers was found infected with SARS^{9,10}.

Sang Ju Yin plus Yu Ping Feng San reported having immunomodulatory effects as it could enhance host defence capacity by modulating functions of T cells¹¹.

Wang et al., reported about the effectiveness of antiviral agents (Remdesivir) and antimalarial agents (chloroquine)in inhibiting the recently emerged novel coronavirus (SARS-CoV-2) pandemic¹². The WHO also endorsed the usage of the same for the treatment of SARS-Cov-2. The important point here is about chloroquine, which is a synthetic analogue of Quinine both being used in the treatment of Malaria.

The role of traditional medicine has been highly appreciated by the government of China to contain and eradicate SARS-CoV-2. National Health Commission of the Republic of China (NHC) reported that 60107 confirmed COVID-19 patients have been treated with Traditional medicine which is 85.2% of total confirmed cases. The report was published on 17thFebruary 2020¹³.

NATURAL COMPOUNDS AGAINST CORONAVIRUS

Plethora of natural compounds from plant and marine sources have been tried and found useful against infections caused by corona virus (SARS-1, MERS, SARS-2) with their mode of action have been included in Table I and Fig. 1. These compounds were found to be from alkaloids, glycosides, flavonoids, Terpenoidal etc. groups. We have also shared the examples from marine sources with the compounds proven to be effective via molecular docking.

II. DISCUSSION

SARS-CoV-2 (Covid-19) infection claiming more than 3, 50,000 lives across the world with over 3.5 million cases emerged as a global threat (Media reports). The current conventional treatment approach includes Antivirals (Nucleoside analogues), immunity modulating agents (Corticosteroids and in severe cases immunoglobulin), antimicrobial compounds (patients with respiratory distress), High flow nasal oxygen or non-invasive ventilation or endotracheal intubation hypoxemic respiratory failure. Recently a combination of nucleoside analogue Remdesivir and antimalarial chloroquine was found effective in controlling Covid-19 at (0.77-1.13 μ M) with high selectivity⁴⁴. Remdesivir was found causing chain termination of viral RNA⁴⁵. Chloroquine, a widely used antimalarial showed efficacy as a potent antiviral agent against and spread. Pre-treatments with chloroquine makes cells refractory to SARS-CoV infection, make cellular environment unfavourable for the virus by increasing endosomal pH and also affects glycosylation process of ACE-2 thus prevents binding of the virus with the host⁴⁶. Still, Deaths are reported worldwide, suggesting there is no cure till date for this ongoing pandemic. Vaccine for preventing the infection remains a distant possibility as WHO cleared that it will take another 12-18 month for the same, hence stressed on adopting preventive measures like social distancing, frequent hand wash with sanitizers or soap and avoidance of contact with wild animals. Several countries including china (Wuhan city being the epicentre) are in lockdown situation to avoid the transfer of the infection.

If going by the current scenario the situation is improved in the Republic of China as along with conventional treatment regimen as discussed above china have included herbal medicinal products Tanrequing (i.m), Shufengjiedu capsules in the treatment regimen of the patients with covid19^{47, 48}. The clinical trial conducted although involved a small number of the patient when compared with the clinical trial with conventional regimen shown better results as a condition of all the patients improved remarkably.

Further, Clinical evidence like case reports, case series, controlled clinical trials and clinical studies, observational studies aiming to observe the effects of traditional medicines supports the importance of traditional medicines in reducing the fatality rates in China, Singapore and Hong Kong during the epidemic of SARS-CoV-1 in 2002. In Hong Kong and Singapore, the fatality rate

reported was 18% while in China it was about 52% initially. The fatality rate was decreased by the date 20th May of 2003 by 4% to 1%. This reduction in fatality rates was mainly attributed due incorporation of traditional remedies along with conventional therapy (antivirals, corticosteroids, oxygen therapy, antibiotics). Not to forget here that most of the antibiotics are also obtained from a natural source which is microbes¹³.

In India, department of AYUSH (Ayurveda Unani Siddha and Homoeopathy) under Ministry of Health and family welfare, have issued an advisory regarding preventing measures which can boost up the immunity with special reference to respiratory health. Some of the measures include Drinking warm water, practising daily the yogasanas, pranayama and meditation. Spices like Turmeric, Cumin, Dhaniya and Garlic in cooking. Apart from this immunity-boosting measures recommended are taking Chyavanprash (An ancient ayurvedic formulation consisting of a mixture of nearly 40 herbs), drinking herbal tea or the decoction made from Tulsi, cinnamon, black pepper, dry ginger and munakka (Raisin). Also advised to take golden milk (Turmeric in milk). In case of cough and cold steam inhalation with mint or bishop's weed and in case of cough with throat irritation administration of clove powder mixed with natural sugar or honey has been recommended⁴⁹.

Recently study carried out by Goswami et al. highlighted high binding capacity ($\Delta G > -30$ kJ/mol of five phenolic terpenoids from *Alpinia officinarum* and three terpenoids (6- Gingerol, 8- Gingerol and 10-Gingerol) from Ginger with SARS- CoV-2PLpro. These being commonly used as spices and treating cough and cold conditions in India could be one of the reasons behind the lower incidences of Covid-19⁴³.

Based on the various studies including the studies which were carried out on natural products against SARS-CoV-1 and MERS-CoV and molecular docking studies published recently (Most of these studies are based on results of experiments conducted on SARS-CoV-1 and MERS-CoV) number of compounds may have potential to be included in treatment ongoing crisis of Covid-19. Natural compounds discussed in this review which are having Anti SARS-CoV and MERS-CoV activity have been tabulated as per their EC50 or IC50 value (Table I). Natural Compound like Baicalin, Scutellarein, Hesperetin, glycyrrhizin and Nicotianamine are reported as potential compounds to prevent binding of the virus with ACE

receptors(ACE2, an enzyme through which the virus is binding with the host cell) must be included in vitro, in vivo studies and clinical trials. Similarly, Emodin blocking the interaction of the SARS-coronavirus spike protein (SARS-CoV S protein) with the angiotensin-converting enzyme 2 (ACE2) must be studied for a possible role in Covid-19. Colchicine can potentially reduce the mortality due to severe pneumonia in Covid-19, hence could be a part of its inclusion in ongoing clinical trials as an immunomodulation agent (Decreases cytokine storm).

Among the natural compounds obtained from fungi and algae (most of the compounds being isolated from marine source), Dieckol (Phlorotannin) isolated from the edible brown algae *Eckloniacavare* reported as one of the most potent SARS-CoV^{pro} phlorotannin inhibitors with $IC_{50} = 2.7\mu M$. Docking studies highlighted that interactions between dieckol and the amino acid residues in the active site of M^{PRO} are mainly constituted by an H-bonds network with a calculated binding energy that is comparable to the energy found by authors with the SARS-CoV-2 M^{PRO} ³⁹. Griffithsin, evaluated via in vivo model was found to be effective pre and post-treatment in SARS-CoV patients with 100% survival rate in mice³⁸. Hart et al., reported strong inhibitory effects of Mycophenolic acid on MERS-CoV in vitro with IC_{50} of 2.87 μM . Also reported that Mycophenolic acid, when combined with interferon, may act synergistically to reduce the viral load⁴⁰.

Apart from structural diversity in natural compounds, one has the liberty to prepare semisynthetic and synthetic derivatives of natural compounds if they are found effective but not potent enough to be utilized for therapeutic measures. N-acetyl glucosamine derivative of glycyrrhizin was most effective among all the derivatives at inhibiting the viral replication of SARS-CoV at EC_{50} of 40 μM with no cell cytotoxicity up to 3000 μM . The β -D-glucopyranosyl β -D-glucuronopyranoside analogue with the changed carbohydrate part, heterocyclic amides of glycyrrhizin, and the acyl hydrazide derivative were active against SARS-CoV with an EC_{50} ranging from 5 μM up to 50 μM . However, these compounds presented high cytotoxicity compared to Glycyrrhizin and its acetyl glucosamine derivative of Glycyrrhizin¹⁹. Cho et al., stated the presence of an unusual 3, 4-dihydro-2H-pyran motif in tomentin molecules was found to be more effective in inhibiting the inhibiting SARS-CoV PL^{PRO} enzyme²¹. Park et al.,

demonstrated SARS-CoV- PL^{PRO} inhibitory activity of curcumin with an IC_{50} value of 5.7 μM . α , β -unsaturated carbonyl derivative of curcumin shown comparable inhibitory activity ($IC_{50} = 6.2$) to that of hirsutenone. In addition to this, authors also observed similar effectiveness of diarylheptanoids in inhibiting SARS-CoV- $3CL^{PRO}$. Furthermore, naphthalene derivatives of hirsutenone ($IC_{50} = 3.0\mu M$) and rubranoside B ($IC_{50} = 7.2\mu M$) were found to be having a greater inhibitory effect on cellular deubiquitinating (DUB) enzymes. A study conducted by Rue et al., have shown SARS-CoV- $3CL^{PRO}$ inhibitory activity of Apigenin with an IC_{50} value of 280.8 μM whereas Gentile et al., projected Apigenin-7-O-neohesperidoside or Rhoifolin with best binding energy (-12.39 kcal/mol) and reported as most promising SARS-CoV-2 M^{PRO} inhibitor in molecular docking study on Marine natural products^{26,44}.

In this review, we tried to compile and classify the plethora of natural compounds such as alkaloids, glycosides, flavonoids, phenolic compounds, terpenoids, tannins and saponin(including compounds from marine sources) according to the sites of their action on viral components of SARS-CoV, MERS-CoV. Few compounds were also found effective against Covid-19. As there is a structural similarity between SARS-CoV-1 and -2, the natural compounds showing anti-SARS-CoV activity may be effective in treating Covid-19 along with conventional treatment regimen. Going by the examples of China and lesser side effects of natural compounds, these may help find the solution to the cause of pandemic Covid-19. Natural compounds have not only demonstrated immunomodulatory effect (hence can be included in preventive treatments) but were also found to be selectively inhibiting RNA dependent RNA polymerase (Preventing replication), target specific chymotrypsin and papain-like Protease inhibitors ($3CL^{PRO}$ and PL^{PRO}), helicase inhibitors, ion channel inhibitors and most importantly also includes ACE-2 binding inhibitors. There are studies like molecular docking pointing towards the effectiveness of the natural compounds in binding these sites hence could be studied not only in direction of using these compounds as adjuvants to conventional regimen but also as the treatment regimen for the Covid-19. Most of these studies are in-vitro, hence proper in-vivo studies need to be carried out followed by clinical trials to establish the full potential of natural compounds. If not found effective in-vivo, chemical modifications to

synthesize derivatives with the help of molecular docking can be taken into consideration as in case of Chloroquine which is semisynthetic derivative to quinine. Another reason to incorporate natural compounds as thrust area against COVID-19 is the unmatched structural diversity among the plethora of natural compounds. Scientist across the globe should think regarding finding a solution in terms of natural compounds for treating the global threat of Covid-19. Believe in the phenomenon, if there is a problem in nature there exist a solution in nature.

III. CONCLUSION

Taking examples from China, the epicentre of a current pandemic of Covid-19, natural compounds should be included as a thrust area for finding the solution. Going by the diverse modes of action of these compounds one need to believe that the solution is around only one need to explore the same. In today's world, it is not at all impossible with facilities of molecular libraries across the world. In the current scenario, respective governments need to incorporate herbal medicines, herbal products to tackle COVID-19 along with conventional treatment regimen. In future, there might be another outbreak so the world needs to be ready with preventive measures such as vaccines which are conventionally regarded as the natural compound. Further going by examples of natural compounds acting on every possible site of viral RNA scientific fraternity need to look towards these compounds as future frontiers in tackling infectious outbreaks such as Covid-19. It is a need of the hour to include these natural compounds along with conventional regiment to treat COVID 19 Patients. The reputed Journal like Nature in its editorial endorsed the use of natural compounds to be used as complementary medicines. As a complementary medicine, they can elevate recovery rates when combined with a conventional treatment regimen (Editorial. Nature: March 2020)

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