IJPSR (2021), Volume 12, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 March 2021; received in revised form, 07 June 2021; accepted, 09 June 2021; published 01 August 2021

NATURAL PRODUCTS AGAINST CORONAVIRUSES

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Keywords:

Antimicrobial resistance, Viruses, SARS- CoV 2, Natural products, Immunity

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ABSTRACT: Background: World Health Organization states that antibacterial/antimicrobial resistance (AMR) can threaten the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi. **Objective:** This review aims to discuss the plants and their derivatives having anti-corona virus/ viral activity. Methods: For the preparation of this review article, all the relevant information was gathered from accessible and inaccessible resources (Web, Books, Thesis, *etc*.). **Results:** It has been accepted worldwide that the uses of herbal products provide stronger immunity which helps to fight against these microbial species. SARS-CoV2 virus is now a pandemic, affecting many countries around the globe. This long series of herbal species may interfere with the target-specific proteins named S Protein, S protein- ACE-2 interaction, Helicase protein, N Protein, $3CL^{pr}$, PL ^{pro} to prevent the viral replication in the host. Traditional herbal medicine not only inhibits the virus attachment to the host body but also prevents replication and boosts up the host immune system. Natural remedies reduce the viral load and, in such conditions, the immunity becomes stronger, and so the patient can recover soon. **Conclusion:** The herbs-natural compounds with antiviral activity can effectively inhibit/blockade the CoV-host protein. Herbal medicine having immune boost-up property will play a major role as an anti-corona virus drug.

INTRODUCTION: Coronavirus is a type of virus that relates to the large family of viruses that causes illness from the very normal cold conditions to headache, throat pain, breathing problems and can also lead to MERS and SARS [1]. Coronavirus has reached more than 210 countries around the globe. More than 2,46,79,975 positive cases have been recognized, while more than 8,36,721 peoples have lost their lives on 28th August 2020 [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(8).4143-50

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(8).4143-50

It was February 2020, and the World health organization used a new name for the critical disease as coronavirus disease or COVID-19 [3]. COVID-19 already has crossed the records of previous outbreaks caused by SARS CoV-1 and MERS CoV-2 [4]. The disease rate of COVID-19 is expanding gradually, yet researchers have not had the option to recommend a particular medication, antibody, or some other affirmed therapeutic specialists against SARS-CoV-2, which subsequently prompts the noteworthy morbidity and mortality [5].

In the lack of newly designed synthetic moieties, the world should move towards herbal moieties as they are showing promising results to overcome the symptoms of the pandemic. One great point of herbal medicaments which makes them an

additional weapon against COVID-19 and antibiotic resistance is that it also increases the immunity of the host which provide proper strength to fight against the virus or microbes [6]. As indicated by the WHO, about 80% of the total populace relies upon therapeutic plants or spices to satisfy their restorative needs. A lot of antiviral mixes created from various sorts of plants have been utilized in numerous examinations. Analysts all around the globe are screening therapeutic medications from existing antiviral plant optional metabolites (PSMs) and are additionally attempting to discover novel mixes from restorative plants to turn away this worldwide emergency.

When we see the mortality rate in the mentioned countries then we found that China has a minimum mortality rate than other more infected countries. The lower mortality rate was proposed in China and the major reason could be the use of herbal remedies or plants from the ancient Traditional Chinese Medicine (TCM) [7, 8]. A performed study demonstrated a very low casualty rate taken up by the SARS-CoV-1 in Beijing when comparison performed with Hong Kong and Singapore [9]. Many COVID clinics in China had utilized a mixture of TCM and conventional medicaments, while Hong Kong and Singapore have used customary medications all through the exploration period. Thus, the scientists found that utilization of an approach could more viably control the contamination and diminish a lot of patient deaths [8]. A Hospital in Beijing, announced that the passing rate of serious patients was 15.4% when a herbal drug combination was utilized, and it was found to be 47% when just conventional medications were applied [9].

2. METHODS: The Literature survey of the proteins which are involved in between host and Corona virus was carried out by searching the previously published articles from the various platforms *e.g.* science direct, google scholar, PubMed, *etc*. Articles were also investigated for the herbal agents which are responsible for inhibition of such kinds of proteins that are responsible for the binding of coronavirus with humans.

2.1. Proteins Involved Between CoV-Host:

2.1.1. S Protein: Protein S is a nutrient K-subordinate plasma glycoprotein orchestrated in the liver. In the course, Protein S exists in two structures: a free structure and a complex structure bound to complement protein C4b-restricting protein. In people, protein S is encoded by the PROS1 quality. The coronavirus S-protein intercedes receptor authoritative and combination of the viral and host cell membranes.[10] CoV utilizes its S, which is called spike glycoprotein, a primary objective for balance counteracting agent, to tie its receptor and intervene film combination and infection passage. Every monomer of S protein contains two subunits, which are S1 & S2.

S proteins of the previous epidemic virus offer around 76% & 97% of AA characters with SARS-CoV and RaTG13; separately, AA succession of potential receptor binding domain of SARS-CoV-2 is only 74% & 90% similar to the SARS-CoV and RaTG13, individually. Recently, performed researches revealed that SARS-CoV-2 uses the ACE-2 enzyme as the target receptor [11].

2.1.2. ACE 2 Receptor: Angiotensin-converting enzyme II is a metallocarboxypeptidase enzyme with similar homology to ACE, a protein since quite a while ago called to be a vital participant in the RAS framework and an objective for the management and treatment of hypertension. It is essentially communicated in the vascular endothelial cells, renal cylindrical epithelium, and in the Leydig cell in the teste [12]. PCR investigation uncovered that ACE-2 is additionally communicated in the lung, kidney, or gastrointestinal a lot previously, tissues appeared to hold SARS-CoV [13]. The significant substrate for ACE-2 is Angiotensin II.20 ACE-2 debases Angiotensin-2 to create Angiotensin 1-7, consequently, contrarily directing RAS.15, 20 this ACE-2 has likewise been appeared to show a safer or protective capacity in the cardiovascular framework and other host organs.

In light of the arrangement similitudes of the RBM among SARS-CoV-2 and SARS-CoV, a few autonomous exploration bunches examined if epidemic virus likewise uses this ACE-2 enzyme as a cell passage receptor. Literature survey indicated that SARS-CoV-2 could utilize ACE-2 from people, Chinese horseshoe bats, civet felines, and pigs to pick up sections into ACE-2-communicating HeLa cells [14].

2.1.3. Helicase Protein: Helicases are a class of enzymes imperative to all creatures. Their fundamental capacity is to unload a creature's qualities. They are engine proteins that move directionally along a nucleic corrosive phosphodiester spine, isolating two tempered nucleic corrosive strands, for example, DNA and RNA, utilizing vitality from ATP hydrolysis. Helicases are promising antiviral medication targets because their enzymatic exercises are basic for viral genome replication, record, and interpretation. Various strong inhibitors of helicases encoded by herpes simplex infection, extreme intense respiratory disorder coronavirus, hepatitis C infection, Japanese encephalitis infection, West Nile infection, and human papillomavirus have been as of late revealed in the logical writing. A few inhibitors have additionally been appeared to diminish viral replication in cell culture and creature models.[15]

2.1.4. N Protein: The nucleocapsid protein of the host (N-protein) is the most plentiful in coronavirus. The N-protein is a previously founded immunogenic phosphoprotein, and it is typically exceptionally preserved. The N protein of coronavirus is regularly utilized as a marker in analytic examines. During virion gathering, N protein ties to viral RNA and prompts the development of the helical nucleocapsid. The bounty and high hydrophilicity of N protein should add to intense resistance after coronavirus disease.

The N protein establishes the main protein present in the nucleocapsid. It is made out of two separate areas, an N-terminal space (NTD) and a C-terminal area (CTD), both fit for restricting RNA *in-vitro*, yet every area utilizes various components to tie RNA. N protein is likewise intensely phosphorylated, and phosphorylation has been proposed to trigger a basic change improving the partiality for viral versus non-viral RNA [16].

2.2. Medicinal Compounds from Nature with their anti-CoV Activities: Nature is the biggest library for active medicinal moieties. For the inhibition of the CoV or its replication, the drug must show activity against the CoV-Host proteins either to inhibit them or to stop their replication in hosts. The scientific survey revealed the following information, which includes the name of the drug against their shown activity has depicted in **Table 1**.

TABLE 1: ACTIVITY OF TESTED NATURAL SUBSTANCES AGAINST CoV AND THE PROTEINS RESPONSIBLE FOR ITS REPLICATION IN HOST

S. no.	Tested natural substance	Result	Reference
1	Beta- galactosidase derivatives of *Quercitin*	Derivative drug was identified as a new drug and a potent inhibitor of SARS-CoV 3CLpro	17
2	Extract of 121 traditional Chinese herbs were tested for their antiviral potency	Extract shows better efficacy and luteolin avidly binded to SARS-CoV Spike-2 (S2) protein without cytotoxic effects. Quercetin also showed antiviral activity with lowcytotoxicity	18
3	26 Isatin derivative from *Isatis Indigotic*	Potent inhibitors of SARS-CoV 3CLPRO while Isatin4o and 4k were especially more potent	19
4	312 controlled Chinese medicinal herbs including emodin	Polygoni multiflora radix, and Polygonimultiflora Caulis inhibited the CoV S protein. Also, emodin blocked the S protein/ACE-2interaction in a dose-dependent manner.	20
5	Aqueous extract of *Houttuynia cordata* were investigated	HC inhibited SARS-CoV 3CLPRO and RdRp. It was also found a better molecule having immunomodulatory properties	21
6	Formulation of 22 medicinal herbs extract	Melia cortex, and Phellodendron cortex, and Sophorasubprostrata radix inhibited viral RNA synthesis, and S and N protein expression.	22
7	12 phytochemicals from *Torreya nucifera*	Alcoholic extract of *Torreya nucifera* showed inhibitory activity against 3CLPRO	23
8	64 Purified natural compounds against helicase protein	Drug ScutellariaBaicalensis has potently inhibited the SARS-CoV helicase protein in *in-vitro* conditions.	24
9	Kaempferol and its glycosidic derivatives	Tested Substances shows the inhibitory action against the 3a Protein.	25
10	Polyphenols from *Roussonetia papyrifera* were tested	Tested polyphenols were potent inhibitors of SARS-PLPRO, and 3CLPRO	26
11	*Tribulus terrestris* fruits Extract and 6 cinnamic amides	All the tested compounds showed the potent inhibitory activity against SARS-CoV PLPRO.	27

12	*Sambucus formosana* Nakai stem and caffeic acid, chlorogenic acid were tested.	*S. formosana* Nakai inhibited HCoV virus and the Caffeic acid was the strongest inhibitor of HCoV-NL63 and powerfully reduced the viral attachment to the host.2	[28]
13	*Strobilanthes cusia* leaves extract and its chemical components were tested.	*S. cusiapotently* inhibited virus yield and viral infectivity of HCoV-NL63 by preventing the viral replication. Indigodole B was the second-highest to reduce HCoV-NL63.	[29]
14	The isolates of Angelica keiskei and 4 coumarins were tested.	The ethanol extract of Angelica keiskei significantly inhibited 3CLPROand PLPRO. It also has shown inhibitory action against the ubiquitin and ubiquitin like proteins.	[30]

Natural Medicinal Compounds with Immune Activity: The immune system is a mindboggling system of cells and proteins that guards the body against contamination. The immune system tracks each germ (organism) it has ever crushed so it can perceive and wreck the microorganism rapidly on the off chance that it enters the body again [31]. Immune backup shields everyone from infections and sicknesses. It delivers an effective antibody to execute the pathogenic matter [32].

In the lack of special medication or immunization against the pandemic virus, one's immune system or protection system is the best guard. The immunity system sup-ports our body's normal capacity to shield against pathogens which include infections, microscopic organisms, parasites, proto-zoan, and worms, resist infections. For whatever length of time that the protection system works smoothly, we don't face infections, bacterial infections as COVID-19. One's immune system can be sorted in three different classes. They are, specifically, innate immunity (fast reaction), versatile immunity (slow reaction), also, detached type of immunity. Uninvolved immunity can also be of two types and they are normal immunity which we get from birth and counterfeit that immunity which we get from medication. Skin and inflammatory reaction start when the body of host is influenced. However, when one's body experiences any kind of pathogen, germs or infections for the 1st time, the immune system can't work appropriately and we become wiped out. Something very similar has occurred on account of Pandemic Virus (COVID) [33]. When the protective cells of one's immune system or protective system become instructed, it completes its occupations by recycling among focal and peripheral lymphoid organs and relocating it and from destinations of injury through blood. Blood conveys gullible and taught immune cells from one site to another, as it streams all through the body, it goes about as a pipeline for the immune system of the host. Cells again go into the bloodstream to be shipped to tissues all through the body subsequent to leaving these nodes through active lymphatic vessels, after being influenced by infection, immune reactions to intervene antibody. T-cells help the B-cells to separate into plasma cells, which consequently produce warrior antibodies explicit to a viral antigen. This antibody is effective in completely obstructing the virus from going into have cells to restrict the infection and assumes a very intense defensive job at the later phase of infection and prevents relapse of infection later on. Conversely, the response of a good immune system can be identified in the infected cells, which are interceded by T-lympho-cytes. The general versatile immune reaction is directed by assistant T cells of the system, while the cytotoxic type of T cells has given a fundamental job in the clearance and removal of the viral-loaded cells [34].

An herb is a plant, or part of a plant that is used for its order taste therapeutic or pharmacological actions [35]. Herbal drugs or botanically origin drugs are used as the supplement of dietary supplements to improve health and wellbeing [36]. These drugs also show and handsome therapeutic profile [37]. Herbal drugs also offer is rainbow of protection to human health as it tends to show medical antioxidant properties example includes ginger, vitamin C, vitamin A, Carotenoids, tulsi *etc.* [38] Herbal antioxidants are also be called as dietary constituents [39]. Antioxidants are supposed to maintain proper body functioning, including the healthy brain, effect on aging, prevent acidification, maintain integrity, maintain cardiovascular system, *etc.* [40] Antioxidants inhibit the free radicals, so they also modulate the immune system of the body [41]. Hence the prevention of the disease takes place [42]. Herbal antioxidants help to activate, boost the immune system and are also used during organ transplantation [43]. So herbs of antioxidants are also used as immunomodulators, and a few of them are mentioned in **Table 2**.

TABLE 2: NATURAL PRODUCTS/ ANTIOXIDANTS WITH THEIR ACTION ON HOST'S IMMUNITY

S. no.	Natural products or natural antioxidants	Immunity Action	References
1	Vitamin A	Vitamin A is basic for the working of T and B lymphocytes. Vitamin A supplementation additionally goes about as an adjuvant, upgrading immune reactions.	44-45
2	β–carotene	Investigations have indicated that carotenoids can improve immune capacities. Carotenoids improved proliferative reactions of T and B lymphocytes. B–carotene also has shown a decrease in tumor trouble.	46
3	Vitamin C	Vitamin C supplementation diminished serum IgE and histamine levels by expanding interferon-c and diminishing interleukin-4 (IL-4), which recommends the concealment of Th2 type immune reaction. Also, it is seen as of clinical use in conditions like atherosclerosis, dominatingly having expanded Th2 cytokine activity.	47
4	*Acorus Calamus*	β-Asarone of *Acorus calamus* works as an enemy of disease reagent in colorectal malignant growth, gastric malignant growth, and lung disease. Its extract has shown antiproliferative and immunosuppressive properties, with excellent antioxidant and antiepileptic actions.	48-51
5	*Ocimumsanctum*	*Ocimumsanctum*or the holy plant Tulsi is believed to show numerous medicinal properties. The Its Extract of *Ocimumsanctum*shows expanded DTH to sheep red platelets SRBCs. Rosmarinic acid is responsible for its antioxidant potency.	52-53
6	Zinc	As in vivo characteristics Zinc supplementation protected the mononuclear cells against the oxidative and it may also lead to downregulation of the inflammatory cytokines. Recently zinc and its supplements are also used as regular supplement to treat the COVID-19 pandemic Patients.	54
7	Curcumin	Curcumin has shown the antioxidant properties and can diminish the gamma radiation-induced toxicity. Curcumin also has shown good effects in CNS neuroinflammatory environment lean to anti-inflammatory response.	55,56
8	Chlorophyllin	Chlorophyllin has demonstrated the cellular protection against the oxidative damage caused by excessive free radicals.	57

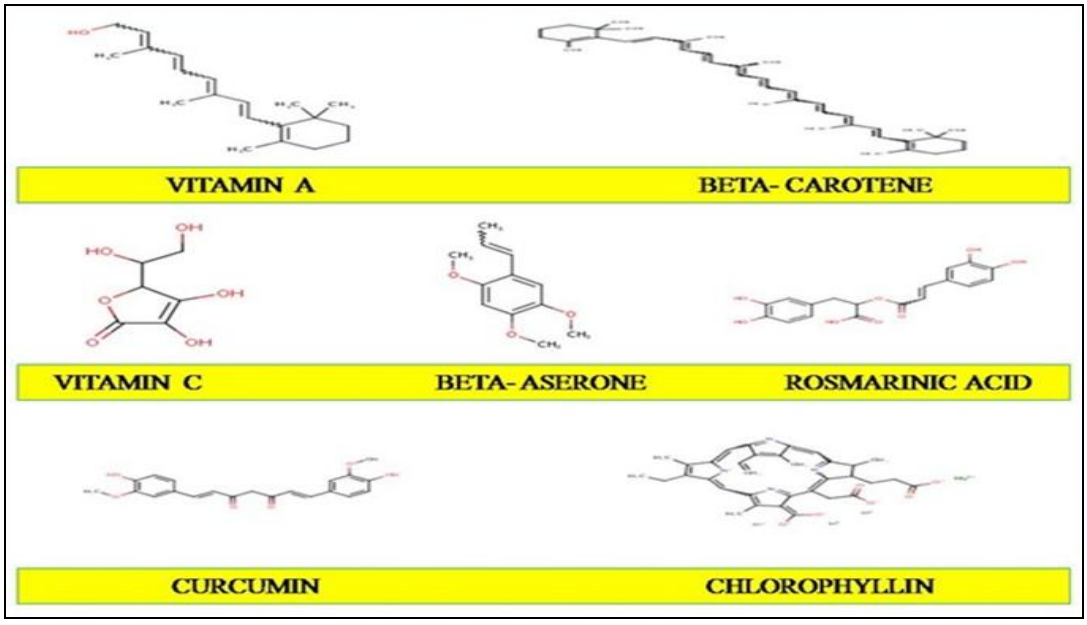

FIG. 1: CHEMICAL STRUCTURES OF FEW NATURAL ANTIOXIDANTS MOIETIES

3. RESULTS AND DISCUSSION: Reviewed studies revealed that natural herbs are very important to treat the patients of COVID-19 because they provide the inhibition of those proteins which are responsible for their replication in host. Additionally, they also improve or boost the immune system. That's the reason these natural herbs are entitled as an additional weapon. **Fig. 2** is given below, which summarize the complete idea of generated thoughts:

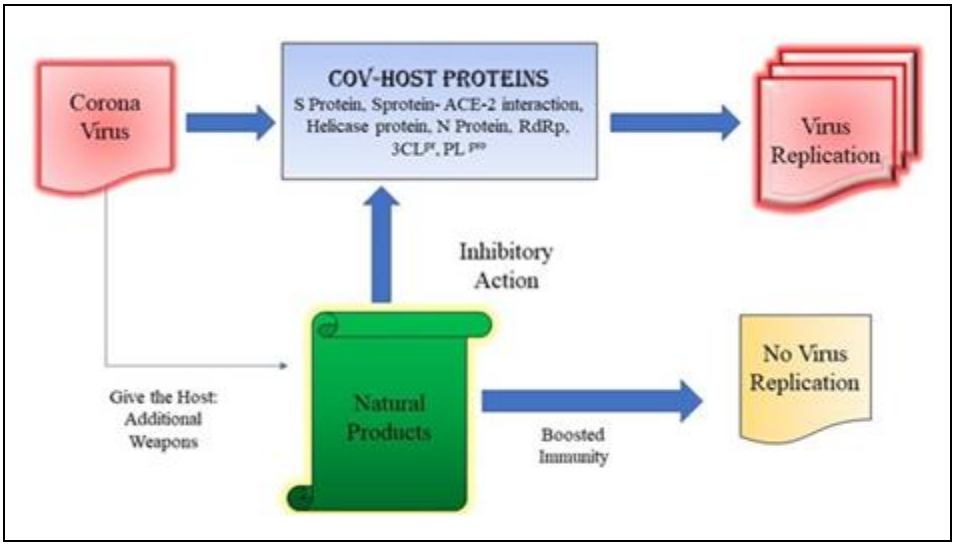

FIG. 2: ROLE OF NATURAL PRODUCTS AS ADDITIONAL WEAPON AGAINST PANDEMIC CoV WITH ADDITION OF BOOSTED IMMUNITY

CONCLUSION: Complete analysis of the previously published articles, treatment strategies clearly mentions that the herbal agents are the basic unit for the rejuvenation of any kind of treatment using any system of medicines. Mentioned herbal agents have been found to be active against the proteins which are working as link between the virus and human beings. Nature is the best healer and it's the only one that has the biggest library of various active chemical ingredients. More and more research should be carried out on such kinds of phytochemicals for the wellbeing of the human world.

ACKNOWLEDGEMENT: Both Authors are highly thankful to their worshipable Parents and NIET, Pharmacy Institute Greater Noida.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest, financial or otherwise.

SOURCE FOR FUNDING: NONE.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL & HUMAN AND ANIMAL RIGHTS: The presented article is a review article and doesn't contain the use of animals/ humans.

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How to cite this article:
Sharma V, Kaushik R, Majee C and Jain J: Natural products against corona viruses. Int J Pharm Sci & Res 2021; 12(8): 4143-50. doi: 10.13040/IJPSR.0975-8232.12(8).4143-50.